REPORT
ON
SPRUE IN INDIA

ARMY HEADQUARTERS

MEDICAL DIRECTORATE

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CONTENTS

PART I

	Page
INTRODUCTION.	
CLINICAL INVESTIGATIONS.	4
Etiological Factors in Sprue.	6
The Clinical picture of Sprue.	10
Symptomatology : The Sprue cycle.	15
Signs of Vitamin Deficiencies.	19
Investigations.	22
Blood Changes.	24
Summary and Discussion of the picture of relapse and remission. ...	28
Conclusions.	30
References.	31

PART II

BIOCHEMICAL ASPECT OF SPRUE.

Section I	
Introduction	33
The measurement of total fat absorption.	33
Variation in fat output.	34
Fat absorption in untreated Sprue.	37
Diarrhoea and fat absorption.	37
Fat absorption in diets of different fat content.	37
The non-fat dry residue.	39
Water content of stools.	39
General characteristics of the fats in the sprue stool. ...	40
Other properties of the Sprue stool.	41
Observations on the chylomicron count charges in Sprue. ...	42
Normal values.	45
Relation between Chylomicron rise and the amount of fat absorbed. ...	45
Fasting values.	47
Chylomicron count in Sprue.	49
Discussion.	50
Summary	50
Fasting serum lipides and fat curves	51
Results.	52
Fasting values in normal and Sprue patients.	53
Changes in the serum lipides after the fat meal.	54
Total fatty acids.	54
Fatty acid fractions.	54
Curves with glycerophosphate, choline, and lecithin. ...	55
Effects of liver treatment	57
Discussion.	57
Summary	58
Absorption of non-fatty substances.	70
Blood Sugar curves.	70
Serum Iron.	71
Section II. (*Nitrogen Metabolism in Sprue*).	
Introduction.	72
Discussion.	74
Summary	75

Section III. (*Salt deficiency in Sprue*). Page

Methods 76
General Clinical features. 78
Laboratory findings. 78
Mineral balance and excretion. 82
Discussion. 86
Therapeutic implications. 86
Summary. 87
Discussion on absorption. 88
Summary of discussion on absorption. 92
References. 93

PART III

CLINICAL RESULTS.

Section I

Criteria of progress. 95
Diet. 97
Caloric Value. 97
Fat content. 97
Carbohydrate Content. 98
Protein Content. 98
Vitamin Content. 100
Results of Parenteral Therapy. 100
(*i*) Effects of nicotinic acid and riboflavine. 100
(*ii*) Effects of parenteral liver. 100
Treatment of Special Symptoms. 102
Salt deficiency. 104
Anaemia. 104
General management of the Sprue patient. 104

Section II. (*Effect of therapy on fat absorption.*)

Effect of Nicotinic acid and riboflavine. 105
Effect of Liver Extract. 106
Yeast Extract. 107

Section III. (*Discussion*)

Section IV. (*Summary*)

References 112
Acknowledgements. 113

REPORT ON SPRUE IN INDIA FROM 1943 TO 1945 FROM ARMY HEADQUARTERS MEDICAL RESEARCH TEAM POONA.

INTRODUCTION

Throughout the campaign in Assam and Burma sprue ranked as a major medical problem. The influx of cases first rose during the fighting around Imphal and Kohima in the winter of 1943-1944. The number of cases remained high (especially early in 1945 around Meiktila) until Rangoon was reached.

The importance of sprue as an invaliding disease is well illustrated by the large number of cases evacuated to the United Kingdom from Feburary 1943 to February 1946 through the Medical Review Board of India. During this period 18,808 cases were reviewed by the Board ; of these 8846 were medical, 5110 surgical and 4852 psychiatric.

More than one fourth of the medical cases were due to amoebic and bacillary dysentery (1254 cases) and sprue (1073 cases). The average period a sprue case spent in hospital before evacuation to England was about one year. It will be obvious, therefore, that sprue was responsible, for a good deal of wastage of man power.

Treatment with high protein diet and liver produced good immediate results, but it was not found possible to retain patients for sufficient time to effect full remission or cure, with the result that many men leaving India still had symptoms, and a variable period of further hospital treatment awaited them before their final disposal could be decided.

This large number of cases presented many problems of diagnosis and treatment. The different opinions regarding aetiology, diagnostic criteria, the methods of dietetic therapy, and the value of liver, all betoken the extent of present medical ignorance on the subject. Lack of sufficient cases and laboratory facilities for adequately controlled investigations have always been two of the stumbling blocks to a further understanding of the aetiology of sprue. In order to make use of the unique opportunity afforded by this large number of patients, an investigation unit was set up in the summer of 1945 by the Medical Directorate, General Headquarters, India. This Sprue Research Team was attached to 3 Indian Base General Hospital (I.B.G.H.) Poona. Since all the cases for evacuation ex-India passed through this hospital, maximal opportunity for collection of cases was here available ; the laboratory work was done in the hospital laboratory and the Central Military Pathological Laboratory.

The following personnel took part in the investigations :—

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MAIN OBJECTS OF INVESTIGATION

The main objects of the investigation were :—

(1) to establish further understanding of aetiological factors by collecting the clinical data at the commencement of the disease, and to clarify its natural history particularly in the interpretation of the significance of its varied symptomatology.

(2) to find out the state of fat absorption under controlled conditions in the disease.

(3) to ascertain the therapeutic effects of liver and other substances under clinical laboratory control.

(1) CLINICAL DATA

Although many clinical studies of tropical sprue have been published, they have dealt almost entirely with the disease as seen in Europeans of long residence in the tropics, or who have returned to temperate climates before coming under close observation. The patients investigated differed notably from the classical sprue in that practically all acquired the disease within three years of reaching India—in many cases, within a year. The duration of symtoms, before observations were made, was in most cases under six moths. This gave the opportunity of observing the early symptoms and the conditions under which they developed. The grouping of symptoms into early primary and later secondary phases have resulted from this aspect of study.

Clinical investigations such as barium meals, fractional test meals and blood counts were done as opportunity permitted. Though limited in their scope, such observations become important when taken in conjunction with the other clinical and bio-chemical aspects of the works

(2) FAT ABSORPTION

While the presence of an increased amount of fat is characteristic of the sprue stool, increased fat excretion cannot be detected with certainty by determining the percentage of fat in random samples of single stools, nor can the progress of a case be followed by this means. Therefore the dietary intake of fat was controlled and total specimens of stool were collected over three or four day periods in sequence. This basic information on fat absorption was supplemented by chylimicron counts and blood fat curves in selected cases. The fat absorption with the absorption of other substances such as glucose and iron was also compared. The second part of this report includes observations on electrolyte and nitrogen metabolism and miscellaneous bio-chemical observations.

(3) THERAPEUTIC TRIALS

Therapeutic trials were carried out from an empirical aspect to determine a practicable method of sprue therapy, and from the viewpoint of etiology since the success or failur of substances in treatment enables some conclusions to be drawn as to pathogenesis. The main body of work concerns liver therapy. Here the chief emphasis has been on defining the manner in which it helps the sprue patient, and the aspects of the sprue syndrome which are not affected by liver treatment. A small number of trials were made with pure B complex vitamins, with vegemite, glycerophosphate, and with sulphaguanidine. The success of diet therapy without the addition of any of the above agents was also studied. No attempt has been made in this

report to give a comprehensive review of the mass of literature on tropical sprue. Much of the older literature deals with discarded theories, and a recent review of sprue literature by Stannus (1942) is already available. The literature directly relevant to the work done in this investigation is covered most conveniently under the separate headings of the report and in the general discussion.

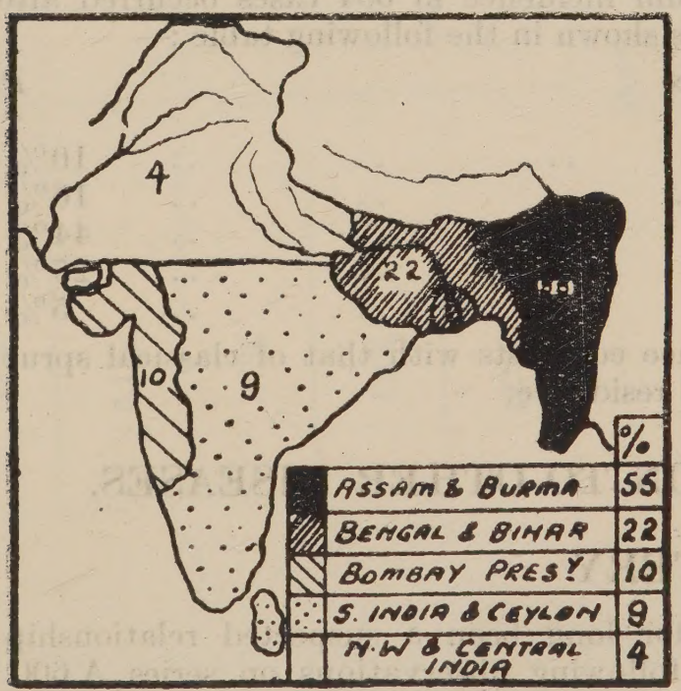
The clinical section of this report is based upon experience of two series of patients. The first consists of more than 600 cases, which were seen in various parts of India during 1943-44 where special laboratory facilities were not available. Observations on these cases are therefore limited to aetiological and other clinical features only. For convenience, this series will be referred to as A.600(2)

The second series of 80 patients comprises those who have been under investigation since June 1945 by the Research Team. The investigations on fat absorption were carried out on 25 cases of this series, and the remainder also were investigated in greater detail than the cases of series A.600. This second series will be referred to as B.80.

PART 1.

CLINICAL INVESTIGATIONS.

Fig 1. SEASONAL INCIDENCE OF SPRUE.



GEOGRAPHICAL DISTRIBUTION
OF 520 CASES IN 1943-5
Fig 2

ETIOLOGICAL FACTORS IE SPRUE

(1) SEASONAL INCIDENCE.

In 1943, 1944 and 1945 until the end of the War, the incidence of sprue was minimal in the cool months of November, December and January, and increased to a pronounced maximum in the hottest months of May and June. Thereafter the incidence fell rapidly in the monsoon period (Fig. 1) This seasonal variation applied to all parts of Burma and Inida.

(2) GEOGRAPHICAL DISTRIBUTION

In Fig 2 is shown the geographical distribution of cases. It will be seen that 55% of cases arose in Burma and Assam, and another 32% in the comparatively small areas of Bengal and Bihar, and the Bombay Presidency. Until the proportion of troops in these areas to those in all India and Burma is known, no inferences can be drawn from these figures.

Within a climatic zone, sprue is regional. Three localities in particular produced many cases as the tide of War passed through, or came close to them. These were Imphal (13% of all cases) in the hill., Chittagong (8%) on the coast near the Ganges delta, and Meiktila (3%) on the plains of Central Burma.

(3) DURATATION OF SERVICE IN INDIA BEFORE THE ONSET OF SPRUE

The maximum incidence in 554 cases occurred after one to two years, service in India as shown in the following table :—

Duration of Service in India	*Percentage of Cases* :—
6 months or less	10%
6 months—1 year.	16%
1—2 years	44%
2—3 years	25%
over 3 years	5%

This incidence contrasts with that of classical sprue, which is associated with long tropical residence.

(4) RELATION TO OTHER DISEASES.

(A) DYSENTERY

There has for long been a suspected relationship between sprue and dysentery. The following observations on series A.600 clarify the issue :—

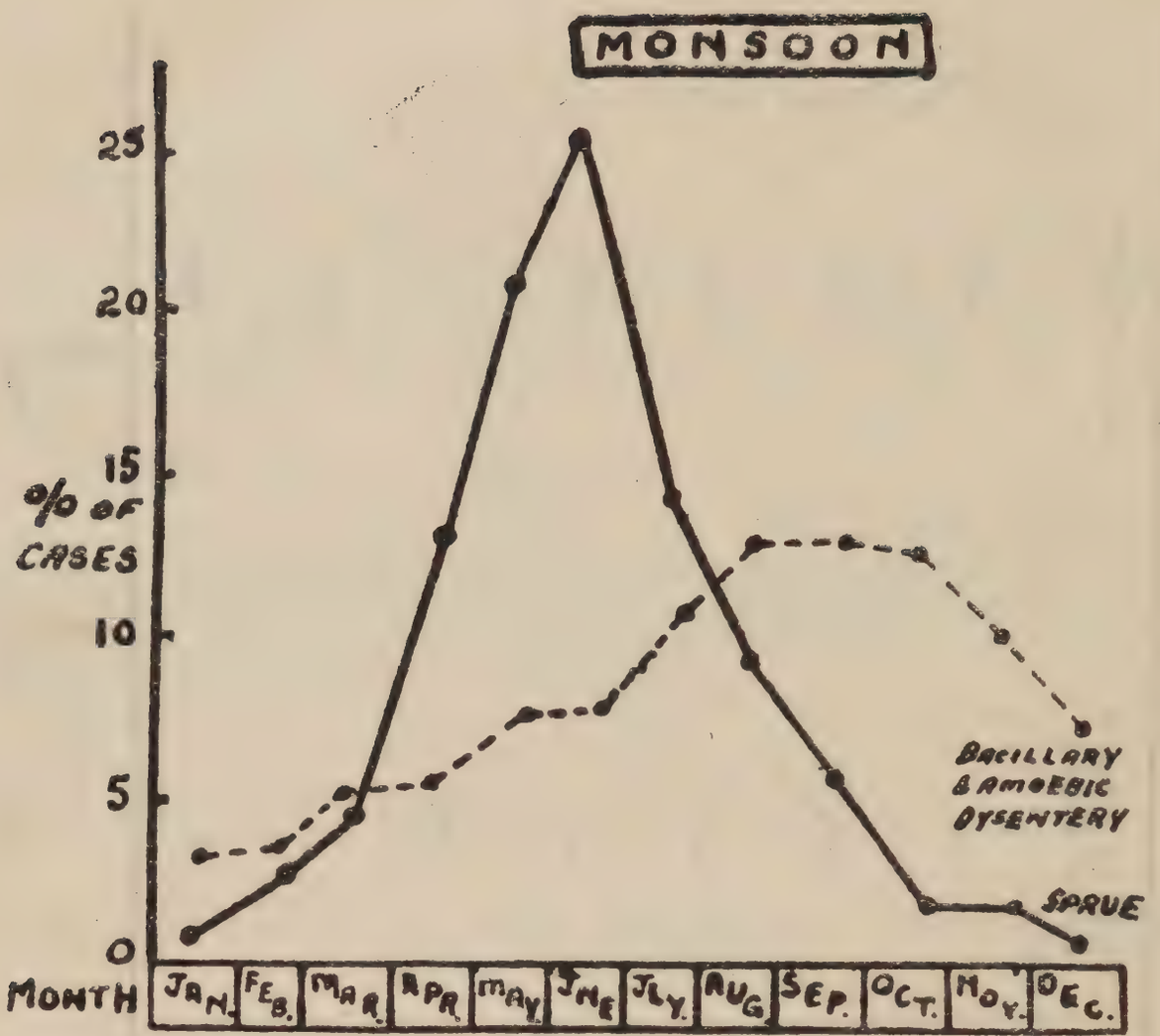
(1) A comparison of the seasonal incidence of sprue and dysentery (amoebic and bacillary) in the same region over the same time is shown in Fig.3. All cases of both diseases were drawn from Assam, North Burma, and Bengal during the years 1943-44. It will be seen that the incidence of sprue precedes that of dysentery surprisingly clearly, in a manner that makes it very unlikely that sprue follows an attack of dysentery at all commonly. The relation to chronic or relapsing dysentery is, or course, not to be derived from such cases.

(2) The incidence of dysentery preceding sprue (23.6%) is shown in table 1. In 16.7% of cases, dysentery had occurred more than one month previously. In 6.9%, it had occurred within one month of the onset. In 340 control cases, the incidence of dysentery in three years, service was 20.8%. The incidence is not significantly high in those with sprue.

INCIDENCE OF DYSENTERY PRECEDING SPRUE (525 CASES) AND IN CONTROL CASES (340).

Dysentery	More than one month before onset of Sprue	Within one month of onset of Sprue.	In control cases
Bacillary	8.0%	2.5%	6.6%
Amoebic	5.1%	3.8%	6.8%
Bacillary & Amoebic.	1.7%	0.2%	2.4%
Clinical	1.9%	0.4%	5.0%
TOTALS	16.7%	6.9%	—
Total Dysentery	23.6%		20.8%
NO DYSENTERY	76.4%		79.2%

Table 1.



COMPARISON OF MONTHLY INCIDENCE OF SPRUE (302 CASES) & DYSENTERY (2200 CASES) IN BENGAL, ASSAM, & N. BURMA IN 1943-4.

Fig. 3.

(3) In individual cases, a close relationship is sometimes found to exist between an attack of amoebic or bacillary dysentery and the sudden passage of typical 'sprue stools' with the development of the full syndrome. It is probable that the effect of dysentery is nonspecific in activating the latent syndrome.

(4) In a few cases who have had repeated attacks of dysentery, steatorrhoea may come on insidously with variable development of the sprue syndrome.

(B) GIARDIASIS.

The occurrence of diarrhoea with pale stools in people infected with Giardia lamblia is well known. In series B.80, six cases had giardiasis before admission to 3 I.B.G.H., and in 2 cases with mild attacks of Diarrhoea, the organism was found in the stools. In these 8 cases, the organism disappeared spontaneously or after a course of mepacrine, without altering the course of the sprue.

(C) MALARIA.

A group of 87 cases labelled "malnutrition" drawn from the Chindit Force in June and July 1944 were found to include 52 patients with the syndrome of sprue. These cases were seen under circumstances that rendered investigation

incomplete, but glossitis with diarrhoea, pale stools, flatulent dyspepsia and marked emaciation were present. Fat analysis of stools in 15 cases showed 12 with faecal fat over 30%. Malaria was found clinically and by positive blood-slide in 42%. Response to sprue therapy in many was unsatisfactory, but improved dramatically after malaria had developed and been treated. This effect of malaria and/or anti-malaria therapy on the sprue syndrome, in these cases, was repeatedly demonstrated. If sprue is present, concommitant latent malaria undoubtedly exacerbates it.

(D) SUBACUTE HEPATIC NECROSIS.

Though subacute hepatic necrosis is not common, several instances of the condition exhibiting the sprue syndrome have been seen at a time when jaundice was absent : bile pigment was absent in the urine but present in the faeces. The sprue symptoms, including the glossitis and steatorrhoea, improved as the liver diminished in size.

(5) DIET.

In series A.600, a large number of troops, including all those from the Chindit Force, developed the sprue syndrome on K rations. The rest were on field service rations, or the basic ration scale, which was introduced in 1944. The course of events was remarkably constant in men from the Chindit Force. For one week the diet was well taken. Then anorexia of increasing degree supervened, followed by diarrhoea two weeks later. Sore tongue appeared after about six weeks on the diet. In some cases, the anorexia became so extreme that the men vomited whilst attempting to eat.

In series B.80, sixty three were on the basic ration scale, although in 36 of these the ration was supplied almost entirely in the form of tinned and dehydrated foods. Another 12 were on K or Compot rations, or a combination of the two. The remaining five form an interesting group in which the onset of sprue coincided with a change from tinned foods to an ordinary or convalescent diet with a good proportion of fresh food.

The approximate composition of these diets is :—

RATION.	CALORIES.	CARBOHYDRATE.	PROTEIN.	FAT.
Basic Ration Scale Compt Ration	4000	530 G	120	155 G
K Ration	3200	430 G	100	130 G

The vitamin content of all the diets is adequate by accepted standards.

In cases who were closely questioned as to feeding habits, irregularity of meals was not a prominent feature.

(6) RACE AND COMPLEXION.

Racial selectivity of sprue is said to be according to pigmentation. The darkest negroes apparently do not get it at all. In dark Indians it is said not to occur, while the brunt of incidence falls on Anglo-Indians and Europeans.

It is undoubtedly true that Indian troops have developed the full syndrome of sprue during the war, though difficulty in diagnosis is increased by the commonness of malnutritional anaemia.

In British troops, though there is no difference in incidence between dark or fair, it is the latter who have provided the great majority of severe cases.

No cases have been seen amongst Jews.

THE CLINICAL PICTURE OF SPRUE.

From the year 1943 to the end of the war, the clinical picture of sprue has differed from that of the classical description of the disease. A brief outline of the clinical types will show clearly where this difference lies.

(1) CLASSICAL SPRUE.

This occurs after long residence in the tropics. In series A.600 10 cases were seen in regular soldiers—mostly officers, whom we have not been able to include in our full investigations. In these patients there was a story of dyspepsia and intermittent diarrhoea over several years, with intervals of months or years between attacks. Sore tongue had been transient. Asthenia and loss of weight, slight at first, had been intermittently progressive until both were marked. Pale stools noticed at first from time to time had recently become constant. Such an officer may have been investigated in hospital more than once, and discharged symptom free. On examination, most cases showed marked emaciation, smooth tongue, achlorhydria probably histamine-fast, distension, diarrhoea with pale, fatty stools, and varying degrees of macrocytic anaemia. Response to treatment was poor.

(2) ACUTE SPRUE.

This term has been used to describe the great majority of cases of both series, which commenced symptoms of sprue within two to three years of reaching India and have progressed to hospitalisation and invaliding within one to two years of the onset. They show therefore, both an early onset in the tropics and a rapid course in comparison with the classical cases above outlined. This course may consist of repeated mild relapses of the condition or may quite suddenly progress into a severe form in which dehydration of a dangerous degree supervenes.

(a) ACUTE SPRUE (MILD)

This group comprises nine out of ten of all cases. The usual story was as follows :—

'The young B.O.R. within a few weeks of arrival in India, has found himself on jungle training. During this time, he has had attacks of diarrhoea, and perhaps one or two bouts of fever. After this he has been sent to Assam and becomes involved in the fighting anywhere between Imphal, Meiktila down to Rangoon. During this period, rations have been for the most part plentiful. Even during periods where supply by air has been the only possible route, shortage of rations was rarely prolonged. After periods of a few weeks to some months on such rations, diarrhoea has developed, often accompanied by anorexia and vomiting, with marked weakness (particularly round Meiktila). Soreness of the tongue later appears with distension and flatulence. The stools may or may not be pale (most are lost in pit latrines). Rapid improvement occurs on hospitalisation with a diagonis of clinical dysentery, with or without sulphaguanidine thereapy ; diarrhoea returns soon after he resumes duty ; the tongue becomes sore again, and the stools pale and bulky. He is again admitted to hospital. As yet, he may not have lost much weight. On hospital diet the tongue clears up, stools regain colour, and by the time he reaches a base hospital there is little abnormal found. Here he may he returned to duty after reducing his medical catagory. After a few more weeks he again relapses, and again is admitted to hospital, where he makes rapid improvement even after stool fats have shown some rise in the accepted normal values. This cycle may continue until further relapse results in his being boarded back to Poona, whence, looking very fit he has been evacuated to England.'

(b) ACUTE SPRUE (SEVERE)

Either from the onset or at some later period, the picture as outlined for a mild case may change into the sundrome of severe sprue. This is characterised by the signs of dehydration. Diarrhoea of moderate to marked intensity is invariably present. Sometimes, 15-20 pale, liquid stools per diem are passed. Anorexia and vomiting are constant owing to which dietary intake of fat is low —stool fat is therefore not markedly raised at this time. Laxity of skin, gross and rapid emaciation, hypotension, soft eye balls, dry tongue often, showing signs of glossitis, are present. Within a few days, the patient becomes drowsy ; the hypotension perists with extreme weakness and prostration and he becomes semi-comatosed. In spite of these advanced signs, response to parenteral liver therapy is obtained, and such cases, though showing 60-70 lbs. loss of weight, have not died but returned to normal wieght in 4-5 months on such therapy.

(3) STEATORRHOEA WITH NO GLOSSITIS (Incomplete (3) Sprue of Manson-Bahr)

Diagnosis in this group of 7 cases from series B.80 has been based on symtoms of anorexia, vomiting, diarrhoea with pale stools and weakness, with a faecal fat greater than 30%. Loss of weight of 20 or more lbs. was present in all. The notable features about these cases have been ;

(*a*) Duration of only one to two months in all seven cases, before hospitalisation and treatment.

(*b*) All cases occurred during the hot season between March and June. Response to dietetic treatment was good in all but one.

In two further cases with similar symptoms and steatorrhoea both commencing in May, but with only 5 lbs. loss of weight, response to diet therapy alone was rapid and satisfactory.

In the earlier series A.600, 3.6% showed this form of the sprue syndrome with good response to diet therapy.

(4) GLOSSITIS WITHOUT STEATORRHOEA (Larval Sprue of Manson-Bahr)

In the series A.600, faecal fat of less than 30% was found in 20% of cases. On analysing this series it was suspected that repeated fat analysis would reduce this percentage considerably. Such was the case in the second series (B.80) in which only six (7.5%) were found with faecal fat persistently less than 30% in the presence of pale stools. In these cases, single-stool fat analysis was used, two to three estimations being performed. Four cases were on a fat diet of 85-95 gms. daily before the fat analysis.

This type of case occurred in men who had been out in India longer than the average, i.e. two to three years (one case eight and a half years). Loss of weight was in all between 20-30 lbs. The glossitis had persisted for 2-3 months before admission, with anorexia, flatulence and distension, and intermittent diarrhoea of three to five pale loose stools daily. Response to sprue diet with nicotinic acid and cooked liver by mouth was not satisfactory. Though the tongues became normal in about one month, and the stools formed and coloured, flatulence and distension persisted, and weight gain was only about 5-10 lbs. In these cases there was no anaemia and Fractional Test meals in all showed normal acid curves.

Prognosis does not appear very good in this type of case. Tendency for the glossitis to relapse is marked, and weight remains low.

(5) TROPICAL SPRUE IN DYSPEPTICS.

A group of six cases in series B.80 was found in which dyspepsia had been a disability for years in England. Two specifically attributed their chronic dyspepsia to fats, and one more voluntered that for one year he had passed pale stools intermittently. All were found to have steatorrhoea within three months of reaching India. One commenced chronic diarrhoea in the Red Sea on the way out, and another immediately on arrival. The possibility that these men had had stestorrhoea in England has to be considered.

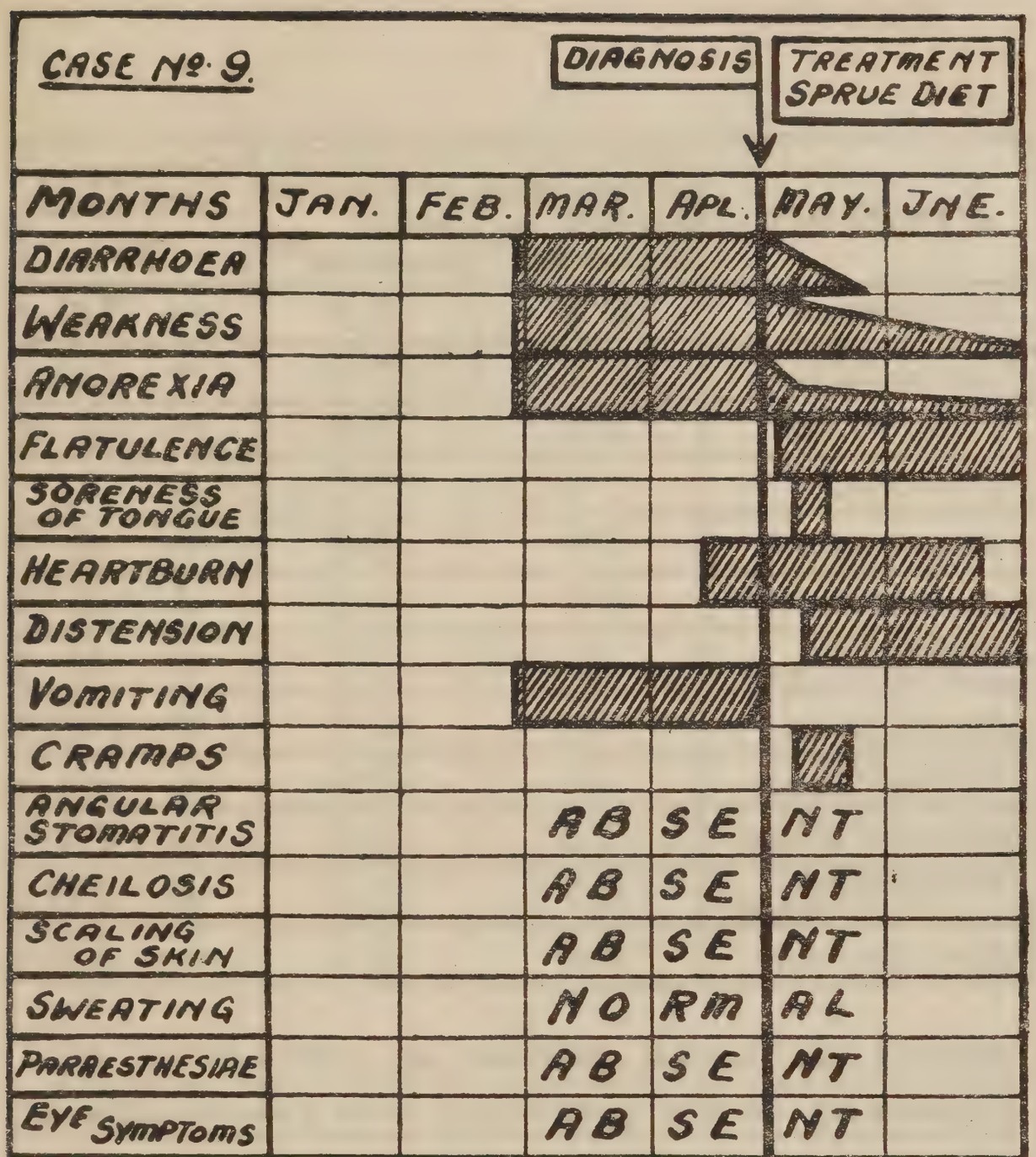


DIAGRAM OF THE TYPICAL CLINICAL PICTURE IN A CASE OF ACUTE SPRUE (MILD)

Fig. 4.

Symptom	Incidence of Symptom Before Diagnosis. %	Incidence of Symptom After Diagnosis %	Change in Incidence %
Diarrhoea	99	69	− 30
Disturbance of Appetite	91	79	− 12
Vomiting	44	38	− 6
Cramps	14	15	+ 1
Weakness	94	98	+ 4
Heartburn	60	65	+ 5
Angular Stomatitis	9	18	+ 9
Cheilosis	5	24	+ 19
Scaling of Skin	9	31	+ 22
Flatulence	73	96	+ 23
Soreness of Tongue	61	90	+ 29
Distension	60	95	+ 35

Chart showing change in incidence of Symptoms after Diagnosis and commencement of Treatment.

Fig. 5.

SYMPTOMATOLOGY : THE SPRUE CYCLE.

The main points in symptomatology are illustrated in Figs. 4&5

Fig. 4 is that of case 9 of series B.80. It shows clearly the grouping of symptoms into two phases which were found well marked in some 85% of cases.

Symptoms of onset consist of anorexia, diarrhoea, vomiting, weakness and loss of weight. Diarrhoea is often but not always first, the remaining symptoms following quickly form a symptom complex that is clear-cut and persists for a few weeks up to two to three months, before a second group of symptoms develops. The chief sign of the second phases is Glossitis which does not occur in the initial phase of onset, appearing only after about 6 weeks in most cases. With glossitis and cheilosis appear other signs, of which abdominal distension is the most prominent. At the time these appear, flatulence and scaling of the skin increase in incidence and in severity. As this second group of symptoms develops, those of onset disappear—appetite returns to normal or to voracity, diarrhoea diminishes or changes to constipation, weakness becomes less intense, and weight loss ceases or tends to increase.

In an untreated patient this remission of diarrhoea and return of large appetite results in increase in food consumption, which within a few days is followed by a return of diarrhoea with the other symptoms of relapse. With relapse the glossitis and distension may decrease but weight is lost again.

This cycle may continue indefinitely with progressive loss of weight to malnutritional levels.

The group of symptoms associated with onset and relapse are similar. They have therefore been described together as "symptoms of onset or relapse".

The second group of symptoms characterised by glossitis and distension, etc., have been grouped as "symptoms of remission", since during this phase the patient has increased appetite, gains weight and shows general clinical improvement.

Fig. 5 shows the change of incidence of symptoms within 2 weeks of commencement of treatment. From the figure it will be seen that though the symptoms of relapse except weakness rapidly diminished in hospital, those have been grouped as the symptoms of remission increased markedly in incidence after admission. At first we failed to understand why after admission and treatment, patients should apparently deteriorate, but on observing relapses which occurred under our own care it was noticed that the sequence—diarrhoea, anorexia and loss of weight—was often followed by sore tongue and increase of distension when the diarrhoea stopped, and appetite improved ; after which, weight gain increased. Such a miniature cycle might be completed in a week.

On a large scale, this cyclic period was found in those cases which came into hospital in relapse and responded to diet therapy. Glossitis produced in this way occurred at the change-over from relapse to remission and lasted from a few days to 2-3 weeks, often clearing on diet therapy alone.

SYMPTOMS OF ONSET OR REALAPSE.

(1) ANOREXIA.

This symptom usually commenced shortly after diarrhoea, and was accompanied by weakness. It was more marked in the evening. Often the only meal of the day to be enjoyed was breakfast. Anorexia may be very marked. One of our cases had been for months diagnosed as anorexia nervosa. Anorexia increases with the severity of the relapse.

(2) VOMITING.

Though common, this symptom is rarely severe in degree. It was most commonly observed in those patients who were worried by gnawing hunger and whose appetite disappeared after a few mouthfuls of food. In such cases the rest of the meal was virtually forced down. Half an hour later the hunger usually returned.

In case of severe relapse, it may seriously increase the dehydrated state of the patient.

(3) DIARRHŒA.

This, almost constantly, was the mode of onset. The diarrhoea may be violent with colic and urgency. Stools were often coloured at first, becoming pale after a variable period. In the same way, there was a variable period between the onset of diarrhoea and that of weakness, anorexia and flatulence. Stools may be frequent, 15-20 per diem. This and the temporary response to sulphaguanidine often led to a diagnosis of "clinical dysentery".

Later the pale liquid stools became firm, as remission occured, and glossitis appeared. Whilst the stools were loose, weight was not gained.

(4) ASTHENIA.

This symptom was found remarkably constant and prominent in the histories of both series of cases. The symptom occured early, often at the commencement of the diarrhoea. In a group of cases arising near Meiktila it preceded all other symptoms by some weeks. Such asthenia is well illustrated in the case of a patient who had to drag himself upstairs by hauling on the handdrail. Dyspnoea palpitation and other symptoms of effort syndrome were not present.

(5) LOSS OF WEIGHT.

Loss of weight is difficult to assess in the tropics owing to the common adjustments that take place in normal men. In 54 healthy men, change in weight after six months in India was found to be as follows :—

Loss of weight in 33 (61%) averaging 8.8 lbs.—Range up to 18 lbs. Gain in weight in 14 (26%) averaging 5.4 lbs.—Range up to 15 lbs. No change in weight—7 (13%).

Normal variation of weight in India is approximately $\pm$ 10% of the body-weight in England. In 47 cases which later developed sprue, change in weight whilst they were in good health was as follows :—

Loss of weight in 18 (38%) averaging 8.5 lbs.—Range up to 19 lbs. Gain in weight in 15 (32%) averaging 6.9 lbs.—Range up to 14 lbs. No change in weight in 14 (30%).

There is thus no evidence of the potential sprue cases having lost weight unduly in India before the onset of the disease.

The degree of loss of weight on admission to hospital in the series A.600 cases was approximately 25% of their English weight.

The most severe emaciation seen was in a patient, whose normal Indian weight was 156 lbs., who was admitted weighing 85 lbs.

TRANSITION FROM RELAPSE TO REMISSION.

It has been stated that when a patient enters remission the symptoms of relapse diminish and disappear. This happens in a clear-cut manner when patients enter hospital in relapse and respond at once to treatment (63% of cases treated by diet alone).

In some, however, the transition is slow. Symptoms of relapse diminish but do not disappear, instead become variable, whilst symptoms of remission appear also vary. In such a patient, appetite varies from day to day—even

from hour to hour, stools vary, a period of mild diarrhoea being followed by a day or two of constipation. Distension and flatulence are distressing—and under these conditions weight is not gained--or rather, a few points slowly gained are rapidly lost again. Glossitis like other signs is persistent though variable during such a period.

Such static cases can be turned into full remission phase with parenteral liver therapy, after one week of which the signs of relapse disappear whilst distension increases, appetite returns, and weight is gained.

With remission induced by liver, glossitis is much less marked than with remission on diet alone.

SYMPTOMS OF REMISSION.

Diminution of the symptoms of the relapse phase will not be further described.

GLOSSITIS AND CHEILOSIS AND ANGULAR STOMATITIS.

Since the word "sprue" describes the sore mouth and tongue it is of Importance to note its place in the 'symptoms sequence' described.

Glossitis was present in over 90% of the cases treated. It will be seen from Fig. 5 that it was present in only 61% of patients before treatment. The increase in incidence occurred on hospital diets—either in those put on a sprue diet because of a discovered steatorrhoea, or on "ordinary" diets.

Thus, many cases diagnosed as steatorrhoea, later, on treatment produced the necessary evidence to change that diagnosis to sprue. Glossitis is thus not an early symptom in many cases. The average duration of diarrhoea in all cases before the onset of glossitis was 3.2 months.

Glossitis appears at the beginning of remission. In fact, it seems to mark the change from relapse to remission. In those cases where it has developed in hospital where observation of associated symptoms has been possible, it has been noticed to coincide with the diminution of the signs of relapse : to last about 2 weeks if sprue diet is continued, during which time appetite improved, distension became more prominent, and stools firm pale and bulky. It disappeared without any addition to the diet therapy, and at this time further gain in weight of the patient was noted. Such a patient usually continued to imporve, and returned to normal weight. In most cases, there was eventually no steatorrhoea, but this was often most marked at the period when glossitis slowly diminished and later when weight was gained. In some however, even with normal weight, steatorrhoea persisted. In cases regaining weight in this manner, glossitis did not return unless there was a relapse—at the end of which it re-appeared in a similar transient fashion.

That glossitis results from simple deficiency of the B group vitamins is known. From this point of view, the diets of 66 cases before and at the time of the onset of glossitis were ascertained, with the following results :—

Diet at onset of Glossitis (66 cases).

(1) Army Basic Ration Scale	43 cases (64%) (21 of these were on Tinned and Dehydrated Rations),
(2) Compo. or K Rations	5 cases (8%)
(3) Hospital Ordinary Diet	9 cases (14%)
(4) Sprue Diet	9 cases (14%)

In the case of diets in hospital, glossitis usually came on within two weeks. But these diets as a whole do not suggest insufficient provision of either calories or vitamins. However, with previous history of anorexia and diarrhoea, it is quite possible that a conditioned deficiency had been produced.

THE APPEARANCE OF THE TONGUE.

In nearly all cases the glossitis was marked by a bright red tongue, sometimes oedematous, and in the early stages, very sore. Smoothness develops quickly, at first due to sub-epithelial oedema with swollen tightpacked papillae. Only later is true depapillation present. Such tongues alter rapidly from day to day. Improvement from fiery red to normal is often observed in less than a week on diet alone.

Fissures have not been a prominent feature. Congenital fissures have been seen to deepen and ulcerate in their depth. Superficial acute fissuring responds, as quickly as the other features of glossitis, to diet therapy. Such fissuring and the typical painful small ulcers of mouth and tongue occur at the height of glossitis.

The "Magenta" tongue of so-called ribo-flavin deficiency was seen on three occasions. In none was this appearance altered by ribo-flavin therapy parenteral or by mouth.

In patients whose condition continually oscillates from relapse to remission, the tongue changes persist over long periods. With each bout of active glossitis there is soreness, and hyperemia. If this recurs frequently before the depapillated tongue has had time to restore its normal structure, then the atrophic smooth tongue appears.

With successful treatment this cycle is stopped. The large majority of tongues returned to normal appearance remarkably quickly in 2-3 weeks. Nevertheless, there is often a period of 1-2 weeks during which the tongue is not sore but shows a smooth tip and sides, and in some cases this smoothness persists for weeks. In all our cases, however, the tongue returned to normal before discharge from hospital.

We could find no correlation between the glossitis and gastric acidity.

Angular stomatitis and cheilosis were less common findings, but they too more than doubled their incidence after admission to hospital—from 9% to 18% with angular stomatitis, and from 5% to 24% with cheilosis. Cheilosis varied with the glossitis ; angular stomatitis developed after glossitis, and responded more slowly to treatment. In several of these cases, dentures have been worn so that our failure to achieve results with parenteral and oral ribo-flavin bears doubtful significance.

ABDOMINAL DISTENSION.

In the onset and relapse phase of sprue, distension of the abdomen is usually absent. This has been particularly noticeable in all our cases admitted with acute severe sprue. Equally remarkable has been the appearance of distension after treatment, coincident with cessation of diarrhoea and vomiting and return of appetite. In this context it is a welcome sign.

In most of the other cases it did not appear for 2-3 months, often at the same time as glossitis, with the cessation of diarrhoea. Unlike glossitis, it persists for weeks or months during remission. It appears to be more closely related to steatorrhoea than any other change, but even this relationship is loose for it has persisted after the stools have become normal in several cases, and conversely steatorrhoea can persist without it.

The mechanism of its production is difficult to understand. Barium meals did not show megacolon or exceptional flatulence in cases with marked distension.

It is increased by increasing the diet unwisely and is in such cases perhaps, of value as a warning that further diet increase will precipitate relapse.

Considering that it is probable that distension is related in some way to absorption from the gut, we have taken its absence as an important criterion of complete remission.

FLATULENCE.

This common symptom occurs to varying degree during the phase of relapse with diarrhoea, but it increased after hospitalisation from 73% to 96% of cases. This increase coincides with an increase of upper abdominal flatulence with belching and heartburn, which appears more marked during early remission.

SKIN CHANGES.

These changes apparently became more marked after admission to hospital. At first it was considered that the increase might be merely a matter of closer observation but further experience made it clear that scaling of the skin with loss of hair are accentuated when the remission phase is entered. Various terms of description have been used by dermatologists to interpret this scaling. These have, however, left us with the conviction that "scaling of the skin" is safest. The features of hyperkeratosis, parakeratosis and follicular hyperkeratosis have been present in varying degree, often lasting about one month and then subsiding as remission progresses. The hair fall out extensively and is general, the size of scale varying from fine branny desquamation to plaques the size of a finger-nail like those seen in ichthyosis.

Pigmentation of the skin was not a prominent sign. Skin signs associated with ribo-flavin deficiency were not seen.

MISCELLANEOUS SYMPTOMS UNRELATED TO REMISSION AND RELAPSE.

CRAMPS AND TETANY.

In series A.600, cramps occurred in calves and thighs in 25%. One case developed tetany. In the series B.80, calves and thigs were almost the only sites in the 14% of cases affected—the symptom usually improved rapidly in hospital. In one case, generalised tetany developed with a total blood Calcium 9 mgm.%. This case simultaneously showed evidence of an acute myopathy affecting the muscles of the shoulder girdle, particularly the delotoids and extensors of the neck, with complete loss of power. No sensory changes were present, and at the time there was generalised loss of reflexes. The patient who had been dangerously ill was responding after 6 days' parenteral liver therapy.

The myopathy and the tetany subsided in one week, without further therapy. This instance strongly reminds one of the myopathic type of case of non-tropical sprue described by Thaysen.[4]

NEUROLOGICAL SIGNS.

Paraesthesiae were absent in all cases. Neurological examination revealed no evidence of motor or sensory change, but tendon reflexes were diminished or absent even in severe cases, as described above in one case, in the presence of tetany.

Mental changes have not been seen.

SIGNS OF VITAMIN DEFICIENCIES.

In series A.600, it was noted that the signs of vitamin deficiency states were limited to glossitis, angular stomatitis, and possibly skin changes. In the absence of any evidence of deficient dark-adaptation, the skin, changes were considered to be of doubtful relation to Vitamin A deficiencies. All these signs cleared remarkably without specific therapy. There were no signs of deficiencies of the fat soluble vitamins D or K, nor of water soluble thiamine or ascorbic acid, and the full syndrome of ribo-flavin deficiency was not seen.

Our observation in series B.80 confirm these findings. In these patients, it was noticed that glossitis, angular stomatitis, and scaling of skin appeared more markedly after treatment in hospital, on either ordinary hospital or sprue diets, both probably adequate in nicotinic and ribo-flavin content.

In our own wards, on an investigation diet used for purposes of therapeutic control, in which nicotinic acid content was 5-10 mgms. and ribo-flavin 3 mgms. cases B. 53 and B.66 showed marked exacerbation of glossitis which cleared in 14 and 10 days respectively without alteration of the diet.

In several instances, patients admitted with glossitis have lost it on this diet without other therapy.

These observations have not supported our expectations of relating the glossitis in sprue to simple nicotinic acid or ribo-flavin deficiency.

It has been noticed that the group of symptoms including glossitis, stomatitis cheilosis and scaling of the skin occur at the beginning of remission phase (see Fig. 4). They are preceded by an onset phase of anorexia, vomiting and diarrhoea which may last some months. At onset, the diets of these patients have been adequate in calorie and vitamin value. If therefore the moath and skin changes are accepted as evidence of vitamin deficiency, it would appear that they are secondary to anorexia, vomiting and diarrhoea in the onset phase of the disease and that they appear most marked at a time when these cond tioning factors are removed, i.e. when appetite returns diarrhoea ceases, and tissue demand increases.

At this time at least some of the capacity for absorption and utilisation of food substances by the tissues is restored, as judged by the fact that on a sutiable diet weight increases. If the diet is adequate in vitamin content, absorption from the gut improves, and tissue utilisation becomes adequate. Such deficiency symptoms as glossitis might be expected to be transient.

In this connection it is of interest to note that with remission induced by liver therapy, glossitis is never marked and often absent altogether. Such a finding suggests that liver contains factors which specifically prevent the glossitis—factors possibly belonging to the vitamin B group.

It would appear that the symptoms of onset may occur with steatorrhoea, and response to therapy be good without glossitis and skin changes ever occuring. Such cases snowing steatorrhoea without glossitis comprise the group termed By Manson-Bahr "incomplete sprue." All 9 such cases in series B.80 were of short duration (1-2 months). Two had lost only 5-10 lbs. in weight ; the others had lost over 20 lbs. in weight. They responded rapidly to diet therapy.

This group of cases suggests that in the early stage of sprue the vitamin deficiency states are not yet developed and remission may occur without any such manifestation.

The incidence of cases of larval sprue (glossitis without steatorrhoea) dropped from 20% in series A.600 to 7.5% in B.80. It is probable that even in this small number steatorrhoea had occurred at some time previously.

These patients too had lost 20-30 lbs. They differed from the group of incomplete sprue cases in that they had been in India longer than average, but were typical in their symptomatology.

CIRCULATORY CHANGES.

Attention has been given to two aspects of the circulatory changes in sprue—cardiac size and hypotension.

CARDIAC SIZE.

Screening and teleradiograms of the heart show that heart size is always within normal limits. It is questionable whether a pathologically small heart can exist, so criteria upon which such a small heart can be diagonosed have not received as much attention as those for cardiac enlargement. It is therefore

SUMMARY OF BARIUM MEAL FINDINGS IN NINE CASES OF SPRUE.

Case	Weight change	Stomach emptied	Mucosal pattern	Region of gut reached in : 1 hour	3 hours	6 hours	Marker time
1 E.B.	--	6 hours	Bolus ++	Caecum	Descendin colon	Sigmoid colon	13 hours.
1 E.B.	++	6 hours	Normal	Ileum	Caecum	Ascending colon	41 hours.
2 H.T.	0	3 hours	Bolus +	Ileum	Ileum	Ascending colon	8 hours.
3 Mc.K.	0	3 hours	Bolus +	Ileum	Ileum	Hepatic flexure	31 hours.
4 R.P.	0	3 hours	Bolus slight	Ileum	Ileum	Ascending colon	-
5 S.C.	0	3 hours	Normal	Ileum	Ileum	Ascending colon	47 hours.
6 S.H.	+	1 hour	Normal	Ileum	Caecum	-	56 hours.
7 J.K.	+	1 hour	Normal	Ileum	Ileum	Splenic flexure	23 hours.
8 V.M.	++	6 hours	Normal	Ileum	Splenic Fexure	Splenic flexure	22 hours.
9 F.H.	-	6 hours	Normal	Hepatic flexure	Splenic flexure	Sigmoid colon	24 hours.

Table 2.

only possible to state that the heart in sprue is "small normal" as judged by screening, cardiothoracic ration and transverse diameters, in 10 cases.

HYPOTENSION.

In series A.600, 8% of cases showed hypotension—arbitrarily defined as a Blood Pressure below 100/70 mm Hg.

In series B.80, such hypotension has been found in 18 cases (22.5.%).

DEHYDRATION.

Twelve acute severe sprue cases showing all the symptoms of relapse with dehydration had hypotension. This persists in some degree usually for about one month after the dehydrated condition has been overcome. In 3 cases only, the blood pressure returned to normal within a week of treatment commencing.

A group of 10 such cases has been further studied regarding electrolyte changes in Part II of this report.

HYPOTENSION WITHOUT DEHYDRATION.

In 6 cases hypotension appeared in mild cases without any acute dehydration phase. It lasted only 2-4 weeks, improving with the patients' weight and general condition.

In such persistently hypotensive patients the low blood pressures are usually stable, not postural, nor are they associated within vasomotor symptoms.

INVESTIGATIONS.

BARIUM MEAL X-RAYS.

Barium meal investigations were carried out on 9 cases. The results are summarised in Table 2.

In all cases the patients were screened and filmed standing, Films were taken using 0.12 seconds exposure with 80-85 K.V. at 15 minutes, 30 minutes, 1 hour, 3 hour, 6 hour and 24 hour. 4 oz. of barium sulphate in watery suspension, free of fat, was used. Each case was given an Iron marker consisting of Ferrous Sulphate gr. 7½ in capsule, at the commencement of the meal, to ascertain the rate of passage through the bowel, as it is not easy to detect barium in the pale sprue stool.

In Table 2, gain or loss of weight occurring up to the time of examination was noted, as this feature closely reflects the general condition of the patient, indicating whether he is in relapse or remission.

Only one patient (case 1 B) was X-rayed whilst in the stage of marked relapse.

RESULTS.

(1) STOMACH EMPTYING TIME.

Often asserted to be prolonged in sprue, this series shows it to be very variable, from 1 to 6 hours, and not correlated with the phase of the disease.

(2) MUSCOSAL PATTERN

This was investigated with full awareness of the variability of normal pattern. For this reason, such appearances as "coarsening of the mucosal folds" were ignored, and almost complete absence of mucosal pattern with gross bolus formation were taken as our criteria of abnormality. Special contrast methods were not available so that finer deviations from normal may well have missed detection.

Case I.E.B. was the most remarkable of the series. At the first examination this man was in severe relapse, with diarrhoea. His weight was 40 lbs. below normal and he was rapidly losing; steatorrhoea at the time was 36%. His X-ray showed no evidence of a mucosal pattern, the barium being shown in 15 and 30 minute films clumped into large masses in the jejunum. Screening showed these masses to be firm; they could not be spread by pressure; they appeared static, and not rapidly progressive though this impression was not consistent with the caecum being reached in 1 hour, and the marker being passed in 13 hours.

The second barium meal was done I month later. At this time he had gained 20 lbs. on sprue diet and parenteral liver therapy. Distension was now marked, and steatorrhoea two days previously had been 50%.

The intestinal pattern is shown in Fig. 6. This shows the difference in the mucosal pattern corresponding to a change from the relapse phase to the second remission phase of the disease with liver therapy.

Cases 2, 3 and 4 also showed bolus formation with little evidence of the feathery distribution of barium. The appearances were less marked than in Case 1. These cases had all been severe. At the time of X-ray they were typical sprue cases, showing steatorrhoea of moderate degree. They were all underweight and not gaining.

Case 5, though static at the time of the barium meal, showed no abnormality of mucosal pattern that we could detect.

Cases 6, 7 and 8 were gaining weight with good appetites. Distension and steatorrhoea were present. Case 8 had been severely ill and was responding very well to liver therapy.

Case 9 was of normal weight at the time of barium meal but steatorrhoea persisted. All the four cases in remission showed apparently normal mucosal patterns.

(3) MOTILITY.

Gross variations in rates of passage through the whole intestinal tract, and various parts of it occur, and it would seem that these are beyond the range of normal. With improvement in appetite and gain in weight, the passage of the barium meal slows down as shown in Casel, and by the fact that in those gaining weight the passage took 23 hours or more.

But this statement does not apply to the rate of passage through the small intestine which remains variable even with improvement of absorption. Case 9 who was chosen by reason of his being of normal weight, practically symptom free, with steatorrhoea only, showed rapid passage of barium to the hepatic flexure in one hour, but the marker was not passed in the stool for 24 hours.

SUMMARY.

The positive X-ray changes on barium meal examination seen in these sprue cases have been

(1) obliteration of mucosal pattern in the jejunum,

(2) bolus formation with aggregation of barium in large lumps and little scatter through the coils of small intestine.

The degree of this change has been found to be related to the severity of the condition. It is more marked when the patient has diarrhoea, anorexia and loss of weight, i.e. is in relapse phase of the disease.

Hypermotility is present in the relapse phase of the disease, though there is stasis in the jejunum at the same time. This hypermotility diminishes in the remission—but remains variable.

Flatulence has not been a prominent feature in these cases. It certainly has not accounted for the marked distension present in the remission phase of the disease.

FRACTIONAL TEST MEALS.

In series A.600, 66% of cases showed normal or hyperchlorhydric curves. Lack of histamine prevented assessment of the frequency of true achlorhydria but hypochlorhydric curves were present in 27%.

Series B.80 showed the following :—

No. of cases	Normal Curves	Hyperchlorhydria	Hypochlorhydria	Achlorhydria Apparent	Achlorhydria True.
66	29 (44%)	13 (20%)	13 (20%)	6 (9%)	

Cases with true histamine fast achlorhydria were all either of long duration i.e. 1-2 years, or instances of severe sprue. Two produced acid after histamine on a later occasion following parenteral liver therapy.

Apparent achlorhydria showed no relation to the severity or duration of the disease.

Hypochlorhydria was associated with diarrhoea, vomiting and flatuence much more commonly than normal or hyperchlorhydric curves. Glossitis was present in 60-65% of these cases at the time of the test meal regardless of the level of the acid curve. It was not more common amongst the achlorhydric group.

Of the barium meal series, which showed bolus formation, case 2 had hypochlorhydria, cases 3 and 4 showed normal curves. In case 1, no test meal could be done.

BLOOD CHANGES.

TECHNIQUE.

All investigations were carried out on venous blood drawn without stasis using Wintrobes mixture as anticoagulant.

Haemoglobin was estimated by Sahlis method. 15 G% was taken as normal.

Erythrocytes were counted in a Neubauers chamber, the blood being diluted with Hayems fluid in a Hawksley pipette.

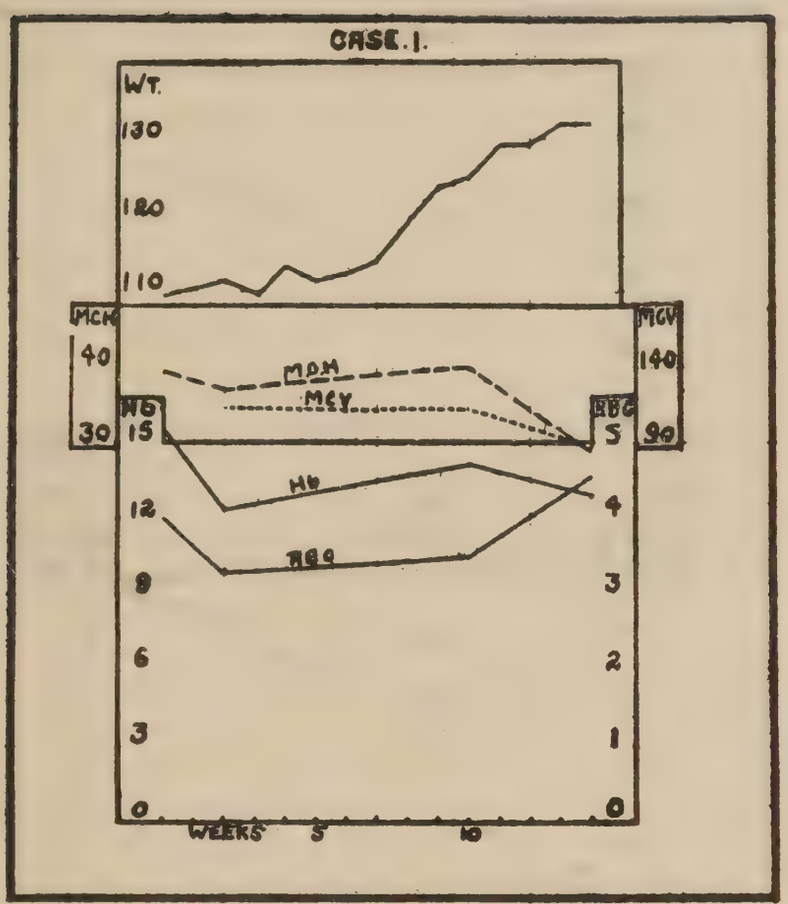
Packed cell volumes were estimated using cut down Westergren tubes (Wintrobes tubes were not available). These tubes being graduated 0-100 were found very suitable, and gave normal results in control cases. The tubes were spun for $\frac{1}{2}$ hour at approximately 2500 revs/min and then for $\frac{1}{4}$ hour at approximately 4,000 revs/min. Readings were taken until a constant value was obtained.

Reticulocytes were counted by the Osgood-Wilhelm technique.

In series A.600, blood counts were grouped according to the haemoglobin level, and a value of less than 12 G% was present in only 24% of cases. At this level, the M.C.H. was minimal (29.577), and variation in haemoglobin in either direction was associated with a rise in M.C.H. No serial blood counts could be done.

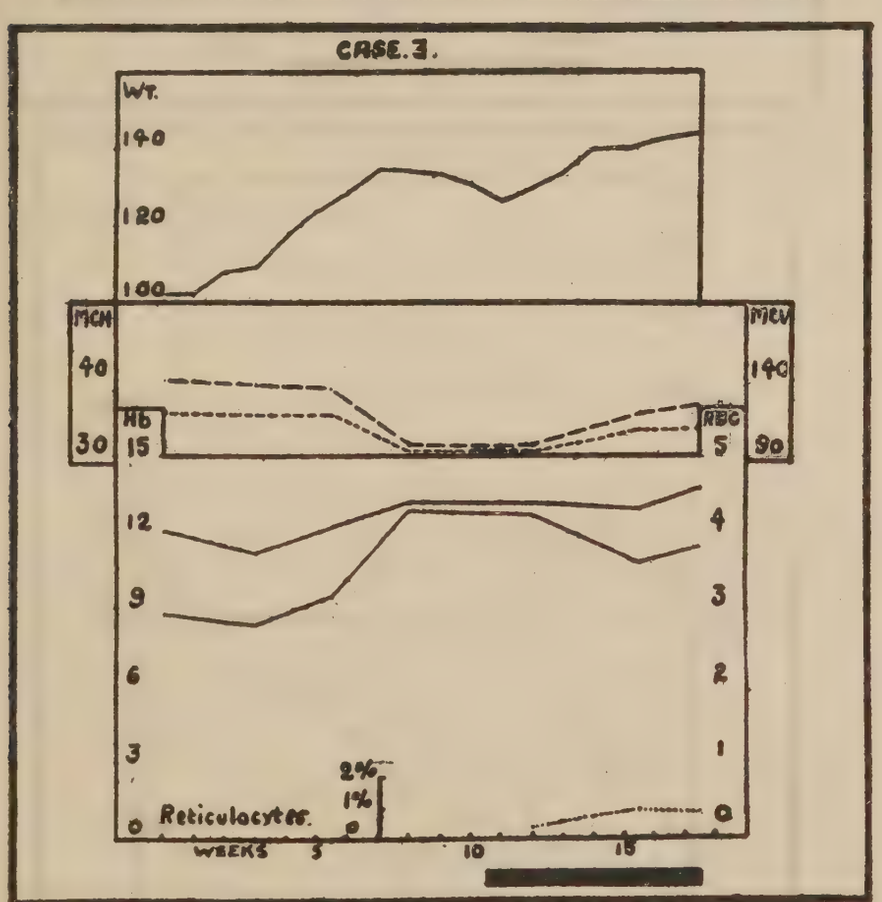
In series B.80, some cases had repeated counts over periods of many weeks. The charts of 4 cases typical of the changes in the blood picture on different forms of therapy are shown in fig. 7.

Case I shows the response in a case treated by sprue diet only. When first seen this case, although at his lowest weight, was not dehydrated and had no anaemia but the M.C.H. and M.C.V. were above normal limits. In 2 weeks a slight macrocytic anaemia had appeared (Haemoglobin level 12.2 gms.%). As the general condition of the case improved (shown by the weight chart), there was little alteration in the blood picture. It was only at the time when gain of weight ceased as normality was reached that the red blood cell count rose, and the blood picture returned to normal limits.

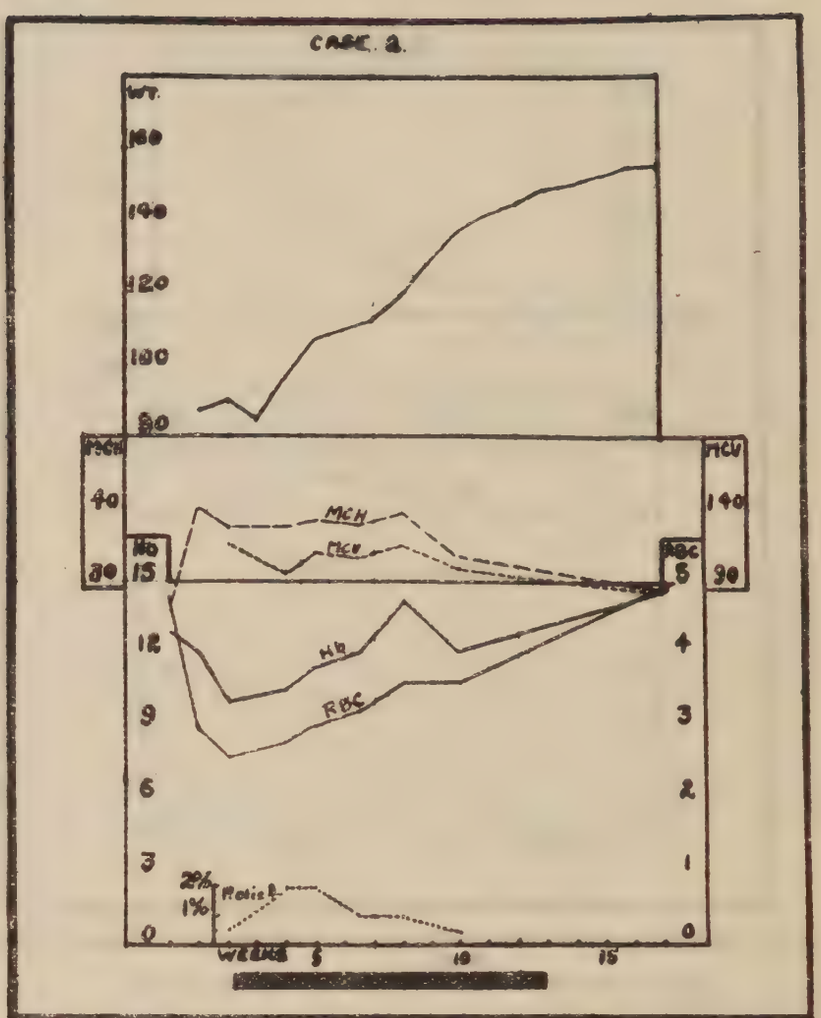


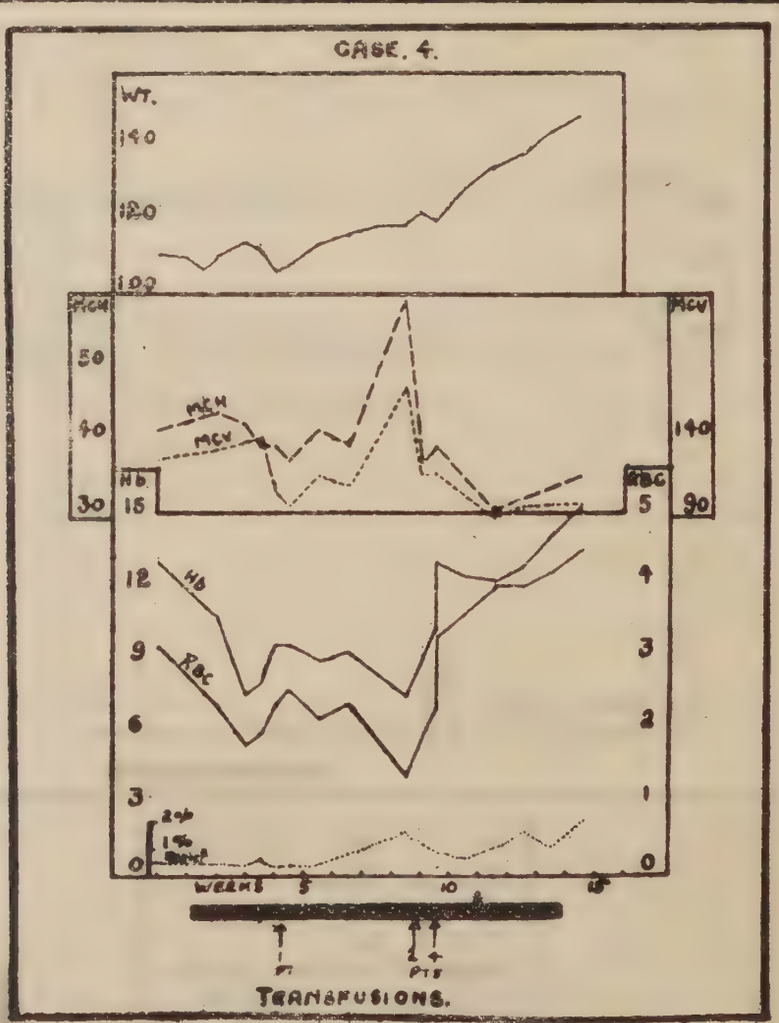
TYPICAL BLOOD PICTURE IN 4 CASES OF ACUTE SPRUE.

Fig. 7.



Hb. in G%. Wt. in lbs.
RBC in M/cmm.
MCH in γγ
MCV in c.μ.
Liver (T.C.F.) 10cc. for 4 days, then 4 cc. daily I.M.





TYPICAL BLOOD PICTURE IN 4 CASES OF ACUTE SPRUE.

Fig. 7

Case 2 was one of acute severe sprue. Although loss of weight was profound (71 lbs.,) the blood picture remained normal until the weight was at its lowest, when a macrocytic anaemia developed. The continued drop in the blood count in the second week when an initial rise of weight occurred and dehydration was corrected, is to be attributed largely to dilution of the blood, as the plasma proteins fell from 5.9 G% in this period. Response to liver therapy was dramatic clinically but improvement in the blood count was slow with persisting macrocytosis, and the maximal reticulocyte response was poor (2%) and delayed (3rd week of therapy). As in Case 1, a return to a normal picture occurred only when the weight was nearly normal.

Case 3 initially showed a persisting mild macrocytic anaemia with clinical improvement on diet therapy. He then had a relapse before normal weight had been reached, but the haemoglobin, and particularly the red blood cell count, rose and the blood picture became normal. This peristed throughout the period of relapse. The relapse was treated with liver therapy and response was good. In spite of this, a drop in the red blood cell count occurred and the blood picture again showed a macrocytosis.

Case 4 was also one of acute severe sprue, with a macrocytic anaemia. Response to liver therapy was poor clinically, and the blood count continued to fall. Accordingly in the 5th week, a blood transfusion of one pint was given —a procedure which had always produced a rapid and permanent response in previous cases of progressive anaemia. In this case, the blood count continued to fall. It is noteworthy that this transfusion produced no immediate effect on the count : this is to be attributed to the clinical improvement (with blood dilution) occurring at the time, following on a period of relapse with dehydration. As the case still failed to respond to usual therapy, two further transfusions of 2 and 4 pints respectively were given. After this the blood picture continued to improve and became normal, and clinical improvement was observed.

The rest of series B.80 have shown similar blood changes. They showed in their initial counts :—

A. Macrocytic anaemia (26%).

B. Normal haemoglobin level and Red Blood Cell count, but macrocytosis (30%).

C. Normal counts (35%).

D. Hypochromic Anaemia (9%).

These later changed in the direction :—Group A to Group B to Group C, i.e., from macrocytic anaemia to normal haemoglobin values with macrocytosis, then finally with complete remission, to normal counts.

Hypochromic anaemia has been uncommon in our experience, 9% only—all were cases of mild sprue which responded to diet therapy alone. Helminthiasis has been found in 3 instances only—one ascariasis, one strongyloides stercoralis, and one ankylostoma duodenale.

The blood changes in these cases of sprue as exemplified above may now be summarised :—

1. In the initial phase of the disease the blood count remains normal for a varying period, often until a profound loss of weight has occurred.

2. The haemoglobin level and the red blood cell count then fall, the latter more markedly, and a macrocytic anaemia is produced.

3. With clinical improvement associated with remission, a slow improvement in the haemoglobin level and cell count occurs, but macrocytosis persists.

4. (a) As the patient approaches normal weight, the red blood cell count rises more rapidly, with fall of M.C.H. and M.C.V., and the blood picture returns to normal.

(b) In a relapse before normal weight is reached, the blood picture improves and may apparently become normal but becomes abnormal again as clinical improvement occurs once more.

5. In dehydrated patients anaemia often appears unexpectedly slight due to haemoconcentration. Conversely the institution of successful therapy often results in an initial fall in the blood count, as dehydration is corrected.

6. Severe anaemia is not correlated with achlorhydria, nor with the degree of glossitis. We have found the degree of glossitis no guide to the severity of the anaemia, but the onset of glossitis often coincides with the appearance of macrocytic anaemia. Both appear during transition from relapse to remission phase. In case treated with liver, the glossitis is absent or slight.

7. Liver therapy appears to exert less influence on the course of the anemia than in pernicious anaemia. Reticulocyte response is usually poor and delayed.

8. In the case with progressive anaemia, one transfusion usually has a dramatic and permanent effect, but rare cases need massive transfusion before a response is obtained.

9. Iron therapy often produces dysepsia and diarrhoea, and is of doubtful value.

Unfortunately, sternal punctures have had to be ommitted.

SUMMARY AND DISCUSSION OF THE PICTURE OF RELAPSE AND REMISSION.

Hitherto, sprue has presented such a diversity of symptoms that its natural history as a disease process has been practically incomprehensible.

Observation of symptoms and signs in these cases has revealed a sequence forming an intelligible pattern in the large majority of cases.

Symptoms may be grouped into (a) those of onset and relapse phase and (b) those of remission phase. These alternate.

Symptoms of onset and relapse are :—

(1) Diarrhoea
(2) Anorexia
(3) Weakness
(4) Vomiting
(5) Loss of weight

} Onset or Relapse Phase.

Symptoms of remission phase are :—

(1) Sore tongue, glossitis, and cheilosis
(2) Distension
(3) Gain of weight
(4) Large appetite
(5) No diarrhoea, sometimes constipation
(6) Increase of flatulence
(7) Scaling of the skin.

} Remission Phase.

In the stage of transition from relapse to remission, various combinations of these symptoms are found.

Fig. 8 shows schematically the progress of a case of sprue from onset to the classical syndrome. The majority of cases described in this paper are Acute Sprue Mild, with apparent recovery after only a few mild relapse phases.

Any of these may however develop, as illustrated, into the severe form of the disease with gross loss of weight and dehydration. It is in this stage that sulphaguanidine, parenteral liver therapy and transfusion are life-saving, and often take the patient straight through remission to apparent recovery.

Classical sprue syndrome probably develops through repeatedcy cles of relapse and remission, with slow steady loss of weight. The diagram covers a period of years.

Malnutrition may thus occur in acute form in the early stages, and again in a chronic form later. It is unlikely that the malnutrition of classical sprue will respond so well to therapy as structural atrophic changes have probably developed.

These two phases are reflected in Barium Meal Examinations, Fractional Test Meals, Blood Picture, and may be summarised as follows :—

	RELAPES PHASE.	REMISSION PHASE.
Barium Meal	Bolus formation Absent Mucosal Pattern Increased Motility (marker time)	No bolus formation. Presence of Mucosal Pattern. Normal Motility (marker time)
Fractional Test Meal	Hypochlorhydria more common	Normal or hyperchlorhydria.
Blood Picture	Anaemia slight, normocytic (Macrocytic in severe cases)	Macrocytic Anaemia.

INTESTINAL ABSORPTION IN RELATION TO RELAPASE AND REMISSION PHASES.

Biochemical investigation carried out on the series B.80 was not designed to compare the condition during these two phases. Cases selected for such investigation were those who had been severely ill or were failing to respond to diet therapy. Cases in severe relapse are medical emergencies and little opportunity exists for investigating this stage. In few instances however, some data was collected, particularly if a patient relapsed whilst under our care.

Cases in marked remission consisted mostly of those who responded well to diet therapy, who were not considered suitable source of the biochemical on absorption which was being sought.

Information on the biochemical aspect of change from relapse to remission is thus scanty. The following changes are briefly mentioned. They are described and discussed in greater detail in Part II of this report.

RELAPSE PHASE

In the presence of diarrhoea of whatever etiology there is diminution of absorption of most if not all food substances. If the diarrhoea in a case of sprue be considered part of the disease, then it may be said that in relapse phase there is marked diminution of fat absorption, as calculated by fat balance tests and chylomicron curves ; of sugar absorption as judged by blood sugar curves ; of protein absorption in one case in relapse on which a nitrogen balance could be done and as judged by low plasma proteins in several. In the case with the negative nitrogen balance this was due to a rise in faecal nitrogen which mght have resulted from primary failure in absorption or from excess of intestinail secretions. Electrolytes are also deficiently absorbed as judged by excess of faecal sodium with low blood levels of this element in a case in severe relapse. Serum iron too in one case was low at the end of relapse phase.

Finally plasma volumes are low in relapse, reflecting the dehydration of this phase.

Thus in relapse phase there is some evidence that a general absorption defect affecting protein, fat, carbohydrate, water and salts is present. To what degree such deficiencies are to be considered specific to sprue could only be assessed by a careful comparison with the changes in other diseases in which diarrhoea is a prominent symptom, for example, proved dysenteries, tuberculous entierties, and malnutrition in temperate climates. Whatever the primary absorption defect in sprue may be, it is rapidly overlaid by secondary deficiencies in the diarrhoeic phases of the disease.

REMISSION PHASE.

This phase can be considered of two types, (a) on diet alone and (b) resulitng from parenteral liver therapy.

(a) Those cases which have gone into satisfactory remission on diet alone have not had complete biochemical investigations. In most of these it can only be said that over a period of 2-3 months, weight steadily increased indicating at least absorption from the bowel adequate for such an occurrence. Fat absorption, as reflected in a drop in steatorrhoea to below 30%, improved in 37 out of 52 cases. Chylomicron curves on such patients are normal. It is probable that any significient improvement in fat absorption occurs late in remission.

Blood sugar curves have not often been done in these cases, nor have other estimations of absorption, so that it is not possible to analyse further changes in patients responding satisfactorily on diet therapy.

REMISSION WITH PARENTERAL LIVER THERAPY

Acute cases in severe dehydration and those failing to develop satisfactory remission on diet therapy alone respond with few exceptions to the addition of parental liver therapy. In such cases we have further biochemical reflections of the induced remission.

FAT ABSORPTION.

This is improved. Such improvoment may be largely if not entirely accounted for by the cessation of diarrhoea, or there may be some specific action resulting in improvement of absorption. In any case, absorption improves but does not become normal, and further improvement during remission beyond about 70-80% of ingested fat is slow.

The chylomicron curve in most cases changes sharply from flat to normal after parenteral liver therapy, i.e. in early remission and not parallel to the improvement of fat absorption.

SUGAR ABSORPTION.

In some cases, the blood sugar curve improves markedly soon after parenteral liver is given, but this is by no means constant.

PROTEIN ABSORPTION.

In all cases where nitrogen balances were done in this stage they showed nitrogen retention, though faecal nitrogen was usually slightly raised. Absorption and utilisation are thus adequate at this stage for weight gain.

Plasma proteins usually show rise early in remission after the dhydration has been overcome.

ELECTROLYTES.

Sodium was still in excess in the faeces one month after liver induced remission had commenced in one case, but blood sodium levels had been restored to normal.

WATER ABSORPTION.

The first action of liver noticed clinically is the production of formed stools as opposed to the watery or creamy diarrhoea of severe relapse. This suggests marked increase of water absorption and coincides with gain of the patient.

CONCLUSIONS

The clinical features of the early symptoms of sprue as seen in British soldiers from 1943-45 have been found to present themselves in two groups.

These have been termed symptoms of onset or relapse, and symptoms of remission. The alternation of these produces the very variable symptomatology of sprue. Where transition from relapse phase to remission is delayed, a mixed picture presents itself. Such patients do not gain weight.

During relapse dehydration is responsible for some of the clinical features found. Barium meal shows gross obliteration of and loss of intestinal mucosal pattern, and absorption of protein, fat, carbohydrate, water and salts is grossly affected. During remission, many of these defects remain for at least one to two months, in spite of rapid gain of weight and marked clinical improvement.

In remission, blood changes consisting of macrocytic anaemia persist until weight returns to normal. Hypotension persists, and may even develop in this phase. Absorption of fats and sugars improves only late after one to two months in spite of liver therapy. Early improvement occurs however in protein absorption and utilisation, and in water absorption.

Signs which may be interpreted as those of avitaminoses A and B group occur at transition from relapse or in early remission.

It will be apparent that remission is in no sense synonymous to cure, for the tendency to relapse appears to remain after clinical restoration to health.

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PART II.

BIOCHEMICAL ASPECT OF SPRUE

BIOCHEMICAL ASPECTS OF SPRUE

Section 1

Introduction

The biochemical approach to the problem of sprue has in general based itself on blood estimations, and on estimations of the percentage of fat in the fresh or dried stool. For example, Hamilton Fairley (1930) carried out estimations of the serum bilirubin, calcium, phosphate and cholesterol, finding low values for the serum cholesterol in most cases. The increase of fat in the stools is often obvious on naked-eye or on microscopic examination, and an increased percentage of fat in radom samples of stools has frequently been reported, as by Sokhey and Malandkar (1928). More recently, Barker and Rhoads (1937), De Langen (1940), and Adlersberg and Sobotka (1943) have used blood-fat curves as an index of fat absorption in sprue.

In this study, we have used three methods of assessing fat absorption-faecal analysis on a controlled diet, the chylomicron count, and blood fat curves after a standard meal.

(a) Feacal Facts

As Pratt (1934) and others have pointed out, in order to study cases of fatty diarrhoea adequately it is necessary to maintain the percentage absorption of fat. As will be seen from the subsequent detailed discussion, this method is well adapted for studying long-term changes in fat absorption but the need to use collection periods of adequate length makes it unsuitable for studying rapid changes in fat absorption.

(b) The Chylomicron Count

This has been extensively used by Frazer (1940) in his important studies on normal fat absorption. It has the important practical advantages of using only finger-prick samples of blood, and of being rapid to carry out. On the other hand, it is difficult to place much quantitative stress on a simple count of particles of very varying size, and the chylomicron count does not show any close correspondence with simultaneous fat estimations in the serum.

(c) Blood Fat curves

Have accordingly been used as the standard method for short-term experiments with the addition to the standard meal of substances which might be expected to influence fat absorption. Blood fat curves do not measure total absorption in the same way as stool fat analyses on a known diet ; but they do give information on the rate of absorption, with limitations to be discussed later.

The biochemical section of this report deals mainly with the information which has been gained by these methods on fat absorption. The absorption of non-fatty substances has also been studied, for comparison with fat absorption. Some more general biochemical observations are also included. The relevance of the information gained in relation to current theroies of the mechanism of sprue is then discussed.

THE MESUREMENT OF TOTAL FAT ABSORPTION.

Since an impairment in the absorption of fat is the most constant and characteristic feature in the biochemical picture of the sprue syndrome, any investigation into the biochemistry of sprue should be firmly based on adequate methods of measuring fat absorption. It is obvious enough that the routine diagnostic procedure of estimating the fat percentage in a dried random sample of stool is quite inadequate for any quantitative survey of fat absorption in sprue ; for it takes no account of the amount of fat in the diet, nor of the variation in fecal fat content from day to day, or even from stool to stool. Even if the fat content of the diet is controlled for some days beforehand, there is still no certainty that a single specimen of stool would represent a fair sample of fat

excretion. It is therefore necessary both to control the diet, and to collect the total faeces over three or four-day periods, and analyse a sample of the well--mixed and weighed stool, expressing the result not as a percentage figure, but as grams of fat excreted per day. This procedure has the advantage that variations in the amount of water left in the stool after routine "drying" do not affect the final result, for any lowering of the fat percentage due to incomplete drying is compensated by an increase in the ratio of dry to wet faecal weight, which is included in the calculation.

The patients undergoing metabolic investigation were put on a weighed diet, and food residues were also weighed. The fat content of the diet was calculated from food tables (McCance and Widdowson, 1936), and the fat content of the main sources of fat in the diet was checked by periodic analysis to ensure that they conformed to the values given in the tables for English foodstuffs. The capricious appetite of sprue patients caused considerable deviations from the planned fat content in some cases ; the appropriate corrections based on the amount of food left over have been made in each case, in calculating the percentage of fat absorption.

The total stools for 3 or 4 day periods were collected in large tin vessels, and preserved with formalin. Carmine and iron markers were used to aid in the demarcation of the periods. The stools were weighed, and thoroughly mixed with a large ladle, and samples of 20-50 g., depending on the wateriness of the stool, were transferred to weighed Petri dishes, and air-dried on a warm surface under a fan. The wet and dry weight of the sample was determined. One gram samples of the dried stool were treated with 30% HCl for 10 minutes in a boiling water-bath, and extracted thrice with ether in a Stokes tube. Tihe ether extract was dried and weighed, to give the fat content of 1 g. of drted stool ; this was multiplied by the total calculated weight of dry stool, to give ehe fat excretion in 3 or 4 days. The fat was redissolved, and the split fat detormined by titration with N/10 alcoholic soda. The percentage fat absorpti ln was calculated from the fat output and the fat content of the diet. This caiculation involves the assumption that true excretion of non-dietary fat is neglgible in comparison with unabsorbed fat derived from the diet ; evidence in favour of this assumption is given later.

VARIATION IN FAT OUTPUT.

When stool collection over consecutive three or four-day periods was begun, it was soon observed that in the same patient on the same diet there was a considerable fluctuation in the fat output from one period to the next. Duplicate estimations showed that the error of actual estimation of the fat content of the dried stool was less than 5 per cent ; whereas the total stool fat in successive periods might vary by 50 per cent or more of the mean value. The variation in the fat content was closely connected with the total weight of dry stool, and it seemed likely that the high results in some periods and the low results in others were caused by a failure of the four day faecal period to correspond accurately to a four day dietary period. When "markers" such as carmine and iron were given in the diet at 4-day intervals, this suspicion was partly confirmed by the different time intervals which elapsed between the giving of the marker, and its passage in the stool ; but although the use of markers did stabilise to some extent the apparent fat output, considerable variations from one period to the next remained. Table I illustrates the effect of markers on the variability of apparent fat output ; it will be seen that even with markers the output of fat is far from constant in successive periods. It must be emphasised that even with markers the "four-day period" is still not a "true" four-day period ; for a marker given with one meal appears in several stools, and also one cannot assume that all constitutents of the diet pass through the bowel at the same speed as the marker. This intrinsic large error in the stool collections makes it necessary to draw conclusions as to changes in faecal fat only from long periods of twelve days or more.

TABLE I.

VARIABILITY OF STOOL FATS WITH & WITHOUT MARKERS.

PATIENT I—*Without Markers.*

Stool total dry weight g./4 days.	Stool total fat g./4 days.	Mean of four Period g./4 days	Standard deviation.	Coefficient of/ variation.
264	96			
203	71	59	+22.6	38.4
83	32			
118	37			
With Markers.				
217	75			
220	53	50.5	+13.9	27.5
107	33			
160	41			
PATIENT II Without Markers.				
132	25			
214	96	48.75	+26.4	54
111	53			
66	21			
With Markers.				
83	34			
264	111	78	+24.6	31.6
156	75			
286	92			

TABLE II

PERCENTAGE FAT ABSORPTION IN UNTREATED CASES OF EARLY SPRUE WITHOUT DIARRHOEA

Patient	Percentage of ingested fat absorbed.	
1	72	
2	51	
3	67	
6	77	
7	78	
8	80	Mean 76%
9	71	
10	73	Range 51% to 89%
12	82	
14	77	
15	79	
16	83	
17	82	
20	70	
21	85	
23	89	
24	77	

TABLE III

PERCENTAGE FAT ABSORPTION IN CONSECUTIVE 12 DAY PERIODS ON PATIENTS NOT RECEIVING SPECIFIC TREATMENT.

Patient	Percentage fat absorption		
	Period 1.	Period 2	Period 3.
6	78	78	75
12	82	88	81
14	77	74	..
15	79	75	..
17	82	83	..
24	77	80	

TABLE IV

PERCENTAGE FAT ABSORPTION WITH AND WITHOUT DIARRHOEA.

Patient.	Without diarrhoea.	With Diarrhoea.
3	67	64
4	80	75
5	73	55
11	61	30
18	73	80

FAT ABSORPTION IN UNTREATED SPRUE.

Table II shows the percentage fat absorption in seventeen patients with early sprue, who were receiving no treatment other than rest and a measured diet containing either 69g. or 96g. of fat per day. Percentage fat absorption was calculated from the expression.

$$\frac{(\text{DIETARY FAT} - \text{EXCRETED FAT}) \times 100}{\text{Dietary Fat}}$$

On a mixed diet with a fat content of 50-100g. of fat per day, normal people absorb 90% or more of the ingested fat. None of the patients with untreated sprue absorbed more than 90% or less than 50%. On an average, three-quarters of the ingested fat was absorbed. Six patients had more than one twelve-day period before treatment was begun, and their figures, given in Table III, show the degree of variation which can be expected in the results of this method in patients not showing spontaneous improvement. Two patients whose later curve showed that they were improving spontaneously without any specific treatment have been excluded from this table. The variation between consecutive 12-day periods is not large, and it is possible with this method to get a satisfactory base-line value for fat absorption, before starting treatment. The method cannot, however, be well applied to patients with watery diarrhoea, in whom the errors in collecting and analysing stools are larger than in patients with formed stools. The effect of various forms of treatment on fat absorption is considered in part III of this report.

DIARROHOEA AND FAT ABSORPTION.

It is well recognised that simple diarrhoea may cause deficient splitting and deficient absorption of fats. (Harrison 1937). We have few data bearing on this matter in our sprue patients, because our general policy was to wait until diarrhoea had cleared up with rest in bed, and in some cases sulphaguandine, before starting a fat balance experiment. Our observations on five patients with diarrhoea, shown in table 4 are therefore to be regarded as incidental, rather than as a planned experiment. Of the five patients, four showed improvement in fat absorption when the diarrhoea was controlled ; the fifth patient had fairly good absorption, even in the phase of diarrhoea. The improvement in fat absorption when the diarrhoea was brought under control with liver treatment is specially striking in patients 5 and 11, who showed the lowest fat absorption before treatment.

FAT ABSORPTION IN DIETS OF DIFFERENT FAT CONTENT (TABLE V)

Five patients who had had a twelve-day period on a diet containing 69g. of fat per day were changed to a diet with 96g. fat per day. In four of them, this moderate increase in fat content of the diet was followed by no greater variation in the percentage of fat absorption than we have observed in the same patient on a constant diet (Table III). The fifth patient, who showed a fall of 7% in his fat absorption, had an initial defect in fat absorption much greater than any of the other patients. The general conclusion to be drawn from this experiment is that a moderate increase in fat intake does not impair the absorption of fat in sprue, unless this is already unusually low. It must be emphasised that the increase in fat intake was purposely limited, and this result has no bearing on the general advisability of restricting the fat intake in cases of sprue.

On a diet containing minimal amounts of fat (6g./day), both normal subjects and patients with sprue excrete very small amounts of fat. The fat which appears in the stools must be mostly secreted fat since it can be assumed that in normal people not more than 1g./day of the 6g. of ingested fat will appear in the stools. The figures given in table VI show that on the 'Fat-free' diet the staetorrhoea in the sprue patients disappears. Findings similar to ours in this respect are quoted by Wintrobe (1942). These results make it unlikely that

a pathological secretion of fat by the intestine plays any significant part in the causation of staetorrhoea in sprue.

TABLE V.

PERCENTAGE FAT ABSORPTION ON DIETS OF DIFFERENT FAT CONTENT.

Patient	Percentage fat absorption	
	69 gm. fat per day	96 gm. fat per day
1	82	83
2	80	74
3	83	88
4	85	87
5	51	44

TABLE VI

FAT EXCRETION (MARKED THREE DAY PERIODS) ON A LOW FAT DIET.

Subject	Period 1	Period 2	Period 3	Period 4
Sprue A ..	41	5.6	6.5	32
Sprue B. ..	75	23	7.3	63
Normal A. ..	15	18	6.1	16
Normal B. ..	21	26	4.2	12

All the figures represent the total fat excretion in g./3 days. In Two periods, 7 and 4, the diet contained 96g. fat/day ; in periods 2 and 3, 6g. fat/day. The high values in period II for three of the subjects are presumably due to "carry over" of stool from period I, in spite of marking.

TABLE VII.

FAT OUTPUT AND NON-FAT DRY RESIDUE IN 12-DAY PERIODS BEFORE AND AFTER TREATMENT.

Patient	Fat (g./12 days)		N. F. D. R. (g./12 days)	
	Before	After	Before	After
2	311	164	303	254
3	376	222	505	487
6	237	105	240	288
7	283	105	400	377
8	235	175	412	397
9	328	179	289	296
14	499	191	418	354
15	286	209	292	340
17	235	139	343	317
24	269	216	612	410

TABLE VIII

Relationship between fat content (% of dry weight), and water content of stools.

Fat (% of dry weight)	Mean water Content (%of non-fat wet weight)	Standard duration of mean
Less than 30 ..	76.9	+6.35
30—40 ..	79.95	+4.39
Over 40 ..	81.5	+6.44

The difference between the means are significant (P less than O.02).

THE NON-FAT DRY RESIDUE

When the total fat in a stool is subtracted from the total dry weight, the total amount of dry stool other than the fat (N.F.D.R.) is obtained. This is very largely composed of bacteria, but it also contains unabsorbed food residues from dietary constituents other than fat. In a given patient on a constant diet without treatment, the N.F.D.R. does not change much, when measured for adequate periods of time. If an unabsorbable food such as a barium meal is given, there is an increase in the N.F.D.R. Table VII shows the total fat and N.F.D.R. in two twelve day periods in ten patients, the first twelve day period being before treatment, and the second after full treatment which has diminished the steatorrhoea. Seven patients had a smaller N.F.D.R. in the second period, the amount of the decrease bearing no quantitative relation to the decrease in steatorrhoea. One patient had no definite change in the N.F.D.R., and two had a rise in the N.F.D.R. although steatorrhoea had diminished in both cases. The higher values for N.F.D.R. in many patients at a period when steatorrhoea is severe may mean that more bacteria are being passed in the stools, or that substances other than fat are being improperly absorbed. From the point of view of practical diagnosis the general trend in N.F.D.R. makes estimation of the percentage fat content of dried stool a less sensitive index of improvement in the steatorrhoea than estimation of total fat excretion.

WATER-CONTENT OF STOOLS

With gross variations in steatorrhoea, such as occur with treatment in sprue, a fair measure of the water content of the stool can not be obtained simply from the ratio of dry to wet stool weight, for the fatty part of the stool is not wetted.

TABLE IX

SPLITTING EFFECT OF NORMAL AND SPRUE STOOLS.

Stool	% fat in Total	Stool split	Weight of wet stool in experiment gm	Weight of mrg. added gm.	Days in incubator.	% of mr. split.
Sprue ..	44.1	42.8	91	36	3	88.8
Sprue ..	23.2	20.5	171	40.2	2	97.3
Sprue ..	41.0	34.8	17.58	2.36	2	90.4
Sprue ..	41.6	33.9	20.29	3.40	2	89.4
Sulphathiaz. & penicillin Sprue ..	41.6	33.9	18.44	2.82	2	54.6
Sulphathiaz. +Penicillin +Cu. So 4. Normal ..	18.4	12.2	52.5	23.5	2	40%
Normal ..	22.4	16.6	12.32	3.40	2	81%

The 'percentage water content' used is therefore derived from (wet weight of stool-fat) and (dry weight of stool-fat). Table VIII shows the average figures derived from sixty-six stools taken at different times from eleven patients with sprue and grouped according to their percentage fat content. It will be seen that stools of higher fat content have also got a higher percentage of water, although the series was limited to formed stools. As pointed out in the previous paragraph, many patients with sprue have a higher non-fat of dry residue when steatorrhoea is gross so that the percentage figures just given minimise rather than exaggerate the total amount of water lost in the more steatorrhoeic stools.

GENERAL CHARACTERISTICS OF THE FATS IN THE SPRUE STOOL.

Considerable attention has been paid in the past to the degree of 'splitting' of the fat in the sprue stool. It has been found that in general the ratio of split to unsplit fat exceeds the normal ratio of 3 or 4 to 1 although occasional stools have been found to contain a larger proportion of neutral fat. The fact that the split fat in the sprue stool generally forms a higher proportion of the total fat than in normal stools has sometimes been taken to imply a defect in the absorption of split as opposed to unsplit fat ; but this neglects the possibility of lipase action in the colon, or in the interval between passage of the stool and analysis (Table IX).

We have found that incubation of margarine with both normal and sprue stools leads to the splitting of the greater part of the added margarine ; if anything, sprue stools are more active in this way than normal stools, probably because of the emulsifying action of the large amount of soap in the sprue stool. The addition of sulphathiazole (1%) and penicillin (20-30 units/ml. of stool) did not inhibit the splitting of margarine, so that aerobic bacterial action is not responsible for the lipdysis. On the other hand, satuarated copper sulphate solution added in the proportion of 5% partly inhabited the splitting. This demonstration of lipolytic activity in the stools prevents any deductions being drawn from the split : unsplit ratio in our material, which consisted of 3 or 4 day specimens. Even in fresh stools it is not possible to say how much of the split fat found may not have been produced during incubation in the colon. The generally observed increase in split fat in sprue stools is best explained on the basis that unsaponifiable fat is the same in normals and sprue patients but the amount of saponifiable fat is much increased in sprue.

TABLE X

NUMBER OF STOOLS WITH GROUPED PERCENTAGE SOAP CONTENT RELATIVE TO PERCENTAGE OF SPLIT FAT IN DRY STOOL

Split fat Total dry weight percent.	Soap fat Split fat percent.		
	under 60	60—80	80—100
20—40	5	11	10
40—60	1	14	5

TABLE XI

STOOL PH GROUPED ACCORDING TO PERCENT OF SPLIT FAT IN THE DRY STOOL.

The figures represent the number of stools in each category.

Split fat	pH			
Dry Stool Weight. per cent	(6.2	6.2—	6.6—	7.0—
(30	11	11	12	6
(30	5	6	17	23

The pH is higher in the more fatty stools, $X^2 = 13.36$, P(0.01.)

We have found that a high proportion of the split fat in the sprue stools is present in the form of soaps, in spite of the fact that most of the stools were acid in reaction. Table X shows the percentage of the split fat occuring as soaps grouped in relation to the total percentage of split fat in forty-six stools from ten sprue patients. The percentage of split fat present as soaps was over 60% in 87% of the stools examined. It can be seen from the table that stools have a high proportion of fat present in the form of soap, irrespective of whether they contain large amounts of split fat or not ; the fixation of electrolytes in the form of soaps will in general increase as the total fat content of the stool increases. A considerable part of the soap in the sprue stool is insoluble in water and in ether, and was found by analysis to contain calcium. On the other hand stools with a higher soap content have been found to be higher in pH than stools of low soap content, suggesting that some of the soap is ionised, and therefore in solution ; we have also found an abnormally high amount of sodium in one formed stool, as an incidental finding in the observations on electrolytes reported later on.

The average molecular weight of the sponifiable fatty acids in eight normal and forty sprue stools was determined by calculation from the weight of the saponifiable fraction, and the titration value of N/10 caustic soda needed for neutralisation. The average molecular weight was 273 in the normal stools and 271 in the sprue stools, the difference not being significant.

OTHER PROPERTIES OF THE SPRUE STOOL.

The pallor of the typical sprue stool has usually been attributed to reduction of bile pigment and to the colourless stercobilinogen. We have confirmed that the total amount of bile pigment in the sprue stool is not abnormally low. Besides the formation of stereobilinoben, the pallor of the sprue stool is also due to its increased bulk, which dilutes the pigment in it. We have found that there is some relationship between the increase in pallor and increase in fat content ; the correlation is not close.

Approximate readings of pH were made on 91 sprue stools, using bromothymol blue and bromocresolpurple indicator papers with B.D.H. capillator standards. The observed range of pH was from 5.8 to 7.4, the average being 6.7 ; these values are less acid than those reported by Thayser (1932). Table XI shows the pH values grouped in relation to the percentage of split fat in the dry stool, the pH is significantly higher in the more fatty stools. This can best be explained by the higher content of soaps in the more fatty stools.

Together with the observations on soap content, these readings of PH suggest that the well known irritant character of very fatty stools is due not to excessive acidity, but to a high content of soluble soaps. The practice of giving calcium salts to diminish diarrhoea has therefore some theoretical justification in that it would increase the proportion of insoluble soaps at the expense of the irritant soluble soaps.

OBSERVATIONS ON THE CHYLOMICRON COUNT CHANGES IN SPRUE.

The blood contains minute particles of fat which are visible by dark ground illumination with high power magnification. These particles were known as haemocomia ; the name chylomicron (Gage & Fish 1924) is now generally used. Changes in the number of particles during the absorption of fat have been studied in normal people by many observers, particularly by Frazer and Stewart (1937).

The speed with which chylomicron curves, after a fatty meal, can be done, and the relatively slight inconvenience to the patient, suggested that the method might be usefully employed in an investigation into fat absorption in sprue. The present report gives the results of 83 chylomicron curves in 28 patients with sprue, together with curves in normal subjects, using the same technique. Other data obtained in the same investigation permit a comparison of the chylomicron count in indiviudal cases with the percentage fat absorption on a controlled diet with blood fat curves, and with glucose tolerance curves. In those cases where several counts have been done at different stages of the disease it has been possible to relate the count to the patient's clinical condition.

The technique used was that of Fraser and Stewart (1937). The fatty meal consisted of 200 cc. of homogenised evaporated milk, containing 18 gm. of fat. It was given after a 12 hour fast. Counts were usually made on serum from specimens of capillary blood, but whenever venous blood had to be taken for other estimations, this was used to provide serum for the count. Frazer (1937) states that except for high counts, counts done on venous blood and capillary blood taken at the same time do not differ.

Counts are made on a small drop of serum spread out by pressure between slide and cover-slip. They are estimated in terms of the number of particles per standard field. Specimens were taken immediately before and at half hourly intervals after the meal, for four or five hours. The first and usually the second half hourly specimens were ommitted.

Capillary tubes about 5 cms. long and of 1 mm. interval diameter were used. These tubes allow satisfactory clot retraction when new, but the clot adheres to the wall if they are used after repeated cleaning. Microscope slides of a standard thickness (1-1.1 mm.) must be used to ensure standard conditions of illumination of the dark ground field. They are cleaned with dichromate solution followed by spirit.

Blood from the finger obtained by a needle stab, is allowed to flow in a continuous column into the capillary tube until it is almost full. The tube is then stuck into plasticine, upright, with the unfilled end uppermost. A slab of plasticine on a microscope slide takes eight or ten specimens for a serial count. After the blood has clotted in the tube, the upper end of the clot is gently freed from the tube wall with a stillette. The clot then retracts leaving a clear column of serum.

It is most convenient to start the count when all the specimens have been collected. A small drop of serum is transferred to a microscope slide by means of finely drawn out capillary. A coverslip is placed on the drop and gently pressed down with a piece of gauze, and any excess of serum is wiped away.

TABLE I NORMAL CHYLOMICRON CURVES

Time	F	1	1½	2	2½	3	3½	4	4½	5 Hours
Subject No. 1	26	14	64	111	180	116	111	120	..	..
2	7	10	55	138	170	40	55	52	..	..
2	20	18	57	77	106	45	39	37	..	..
3	74	34	94	136	135	124	66	35	..	..
3	40	83	132	140	162	107	45	28	48	21
4	8	..	58	94	119	122	61	60	..	..
5	20	..	49	95	142	118	131	86	..	..
6	9	..	34	53	80	105	70	47	43	23
7	2	6	34	54	58	137	109	42	57	39
8	6	15	46	73	125	68	123	83	76	37
8	16	..	89	105	143	137	166	75	54	35
8	2	..	..	128	97	90	44	33	..	10
9	4	90	105	270	200	140	70	160	40	15
10	15	..	125	185	140	105	85	20	..	..
11	1	..	15	20	20	100	30	40	..	..
3	5	..	..	150	230	140	..	30	..	..
8	10	..	30	110	130	70	60	5	5	..
7	5	..	80	70	120	110	80	35	20	15

TABLE II CURVES ON ONE PERSON AFTER VARYING QUANTITIES OF FAT

Time	F	1	1½	2	2½	3	3½	4	4½	5	Av. at peak
9 gm.	13	12	65	85	30	80	45	7	8	..	60
18 gm.	74	34	94	136	135	124	66	35	..	..	132
18 gm.	40	83	132	140	162	107	45	28	48	21	136
18. gm.	5	..	..	150	230	140	..	30	..	..	173
36 gm.	23	135	190	270	410	380	325	190	215	..	372
36 gm.	5	8	74	165	190	330	310	125	..	..	277

TABLE III EFFECT OF CALCIUM SALT ON CHYLOMICRON CURVES SIMPLE MILK MEAL

PF	74	34	94	135	135	124	66	35	..	*
DB	20	18	57	77	106	45	39	37	..	@
PM	10	..	30	110	130	70	60	5	5	..
PR	6	..	80	70	120	110	80	35	20	15

MEAL WITH CALCIUM SALT

PF	13	10	20	28	80	80	42	4	..	..	0
DB	9	6	9	28	47	80	30	25	..	..	0
PM	70	...	7	20	43	25	25	15	10	10	+
PR	5	..	15	15	..	50	20	15	10	—	+

* Lowest of three curves on this subject.

\+ Lower of 2 curves on this subject.

* With 10 mg. Calcium Glycerophosphate

\+ With 7 gm. Calcium Lactate.

TABLE IV EFFECT OF CALCIUM SALTS ON FAT ABSORPTION

Average daily total fat content of stool

	During 6 days before giving Ca. Lactate.	During 6 days of Ca. Lactate Administration	During 8 days after giving Ca. Lactate.
PM	9.3 gm.	11.8	11.6
PR	4.3 gm.	8	6.4

TABLE V RELATION BETWEEN HEIGHT OF CHYLOMICRON COUNT AND PERCENTAGE OF INGESTED FAT ABSORBED.

	% dietary fat absorbed.				
	60	60—	70—	80—	Total
Chylo. Peak .. 100	3	5	5	4	17
Count. .. 100	3	4	6	8	21
Total	6	9	11	12	38

TABLE VI ASSOCIATION BETWEEN CHYLOMICRON PEAK AND TOTAL FATTY ACID INCREMENT

Total fat mg. %	40	40
Chylos. 100	12	3
100	7	15
TOTAL	19	18

$X2 = 6.26$ $P = 0.02$

The depth of such a film of fluid, which causes the two glass surfaces to adhere, is determined mainly by the physical properties of the fluid and is reasonably constant.

In examining the preparation by dark ground illumination particular care must be taken to secure optimal illumination since, with inadequate light, excessively thick slides, or a condenser badly centred or focussed, false low counts will be reported. With satisfactory lighting the fow red cells present show up as a uniformly bright ring of light. The chylomicrons are refractile, about in diameter and show rapid Brownian movement. They may be confused with igranules from leucocytes, but such granules, unlike the chylomicrons, have a dark centre. Particles indistinguishable, except by their immobility, from chylomicrons may be seen fixed to the slide or coverslip but they are relatively few when clean glassware is used. Since many may be seen in preparations known to contain few chylomicrons, they are ignored in making the count.

The standard field on which the counts were based was that obtained with a 1/12 inch objective and X15 eyepiece. Up to fifty chylomicrons can be counted in such a field ; but when the counts rise to higher numbers, a smaller field is used. This was obtained by inserting a diaphragm in the eye-piece, giving an area one fifth of the large field. Such a diaphragm may easily be made from paper cut into a disc from which a section with an angle of 72 degrees has been cut out.

The chylomicrons are counted to the nearest five and at least five large or ten small fields should be counted and the average taken because the particles are not quite evenly distributed in the preparation. The count is made on only one depth of focus. For a given observer the variation found in doing several counts on different preparations made from the same specimens of serum is about + 15%. Since the smallest particles are invisible, and only those are counted which are definitely visible, there is a large subjective element in estimating the count. The great variation in particle diameter, implying a variation in particle volume of several hundredfold, makes these sources of error comparatively negligible when attempting to use the count as an index of fat absorption, since no allowance is made for variation in particle size.

NORMAL VALUES.

Eighteen curves done on eleven normal men with the standard meal are shown in Table I. The fasting counts vary between 1 and 74. Only three are over twenty. The time of the peak value of the count after the meal is fairly constant and in all the curves lies between two and three and a half hours and is at two and half hours in ten of the curves. The peak value is very variable, averaging 150 (SD+ 43.5, range 100-270). The height of the peak may vary by more than 50% from time to time in the same person.

These results are comparable to those obtained by Frazer who found that the curve reached a maximum rise in 2½ hours. He found somewhat higher counts and this may be attributed to the use of a different meal.

RELATION BETWEEN CHYLOMICRON RISE AND THE AMOUNT OF FAT ABSORBED.

Changes in the curve in the same perons caused by varying the test dose of fat are shown in Table II. Halving the standard dose of fat, produced a lower peak and doubling the dose, a markedly higher peak. This relationship provided evidence that the increase in the number of chylomicrons during fat absorption is due to absorbed fat, and the question arises whether the height of rise depends on the total amount of fat absorbed, on the rate of absorption or on the form in which the fat appears in the blood stream.

It was found that when a soluble calcium is given with the standard meal a low chylomicron curve results (Table III).

TABLE VII ASSOCIATION BETWEEN CHYLOMICRON PEAK AND PHOSPHOLIPID INCREMENT.

PL.mg.		.5	.5
Chylo :	100	8	7
	100	9	13
TOTAL	..	17	20

X = 0.17 P = 0.7

TABLE VIII DISTRIBUTION OF THREE TYPES OF CHYLOMICRON CURVE IN SPRUE.

Type of curve	Without liver		With liver		
	Without diarrhoea	With diarrhoea	Without diarrhoea	With diarrhoea	Total
I	8	11	0	4	23
II	18	2	7	0	27
III	23	0	13	1	37
TOTAL ..	49	13	20	5	87

TABLE IX DISTRIBUTION OF FIRST CURVE ON EACH PATIENT.

Type of	Without liver		With liver		
	Without diarrhoea	With diarrhoea	Without diarrhoea	With diarrhoea	Total
I	3	3	0	0	6
II	9	1	0	0	10
III	11	0	1	1	13
TOTAL	23	4	1	1	29

To determine whether the low chylomicron count corresponded to a diminution in the amount of fat absorbed, a balance experiment on two normal subjects (PM & PR) was carried out. The diet contained 95 gm. of fat per day and 30 gm. of calcium lactate were given per day in divided doses, with each meal, for six days. A carmine stool marker was given at the beginning and at the end of the six day period, and the total fat in the stools for that period and for periods before and after the experiment was estimated. The results of the experiment are shown in table IV.

It will be seen that though $7\frac{1}{2}$ grams of calcium given with the standard meal produced in these subjects low curves, this dose of calcium given four times a day with a diet containing 95 gms of fat per day did not produce steato-

rrhea. The low chylomicron counts observed with calcium lactate reflect either a change in the rate of fat absorption or a change in the form in which the fat appears in the blood stream, but do not indicate a gross diminution in the total amount of fat absorbed.

Further evidence on the relation between chylomicron count and the total amount of fat absorbed is derived from 38 curves on sprue patients whose fat intake and output was being measured (Table V).

The chylomicron curves have been grouped according to the peak value, above and below 100. Of the 17 curves with a peak below 100, eleven had a peak below 80. The table shows that while an abnormally low chylomicron count is common when fat absorption is poor, the incidence of low counts is not quantitatively related to the severity of the fat absorption defect. A normal count is common when 30% of the ingested fat is not being absorbed, as in an average case of sprue. This high proportion of normal curves with definite steatorrhoea is not surprising when it is considered that the greater proportion of ingested fat is being absorbed. On three occasions however, normal curves were found when only 50-60% of the ingested fat was being absorbed. Such cases suggest that chylomicrons may represent only a fraction of the blood fat, the level of which may rise during fat absorption though total fat absorption be poor.

A study of 37 chylomicron counts done concurrently with serum fat curves in which the total fatty acids, total cholesterol and lipid phosphorus were estimated, might be expected to show whether chylomicrons are derived from any of the recognised fractions of the blood lipids. The serum lipid estimations were done as part of a study of intestinal absorption in sprue and are to be reported in full in another section of the report.

FASTING VALUES.

The fasting values of the chylomicron curves in the fat curve series fell into two groups : thirty one were under thirty and six were over forty.

No significant difference was found in the fasting values for total fatty acid, phospholipids or total cholesterol in these two groups.

CURVES.

In relating the chylomicron counts to the changes in the serum lipid fractions during fat absorption, the fasting value of each lipid fraction has been deducted from the subsequent values of the curve, so as to minimize the effect of the variation due to the widely differing fasting values. No such correction has been applied to the chylomicron counts, since in most cases with a fasting count, the count drops before rising to the usual peak. Moreover for the peak values the correction to be applied would in most cases be less than the error of the count.

Table VI shows a significant association between the increment in total fatty acids and the height of the peak of the chylomicron count. The total fatty acids consist of neutral phospholipid and cholesterol-bound fractions. Table VII shows no significant association between the chylomicron peak value and the phospholipid rise ; increments in the total blood cholesterol when they occurred were too small to account for except for a fraction of the total fatty acid increment. On the other hand the association of the chylomicron peak value with the neutral fat rise was found to be at least as strong as that with the total fatty acid increment. With values derived from 34 curves, 9 normal and the rest from sprue cases, the correlation coefficient for the two association were found to be, for the neutral fat increment 0.378 ; for the total fat increment 0.331. The standard error of these two co-efficients is 0.17, hence only the first is in fact statistically significant. The fat curves and corresponding chylomicron counts from which these correlation coefficients have been derived are given in another section of this report.

TABLE X EFFECT OF LIVER THERAPY ON THE CHYLOMICRON CURVE

Name	Liver therapy date.	chylo date	F	1	1½	2	2½	3	3½	4	4½	1% fat absorbed
NORRIS	5-8th June 40 c.c. Liver.	4.6.45	11	13	5	18	47	49	41	50	44	
		9.6.45	3	10	8	17	30	53	66	96	106	
		13.6.45	10	9	18	17	53	51	77	51	82	
		21.6.45	31	5	25	70	68	100	135	81	88	
CASS	1.8.45	19.7.45	5	..	8	25	89	89	73	56	25	approx. 50
		8.8.45	20	..	6	25	70	130	90	75	50	53
COLLIER	6.1.45	3.1.46	3	..	..	..	40	50	50	20	..	57
		24.1.48	2	10	100	200	150	100	50	50	..	82
BURTON	16.1.46	7.1.46	58	..	..	..	46	65	43	44	..	88
		24.1.46	12	10	50	50	40	120	50	20	..	86

TABLE XI ASSOCIATION BETWEEN TYPE OF CURVE AND WEIGHT GAINED

Curve type	Loosing Weight	Weight steady	Gaining Weight
I	3	2	1
II	1	11	3
III	1	11	6

TABLE XII ASSOCIATION BETWEEN TYPE OF CHYLOMICRON CURVE AND GLUCOSE CURVE.

	Chylomicron peak 100	Chylomicron peak. 100	Total
Blood glucose increment. 34	11	6	17
Blood glucose increment. 34	5	13	18
TOTAL : ..	16	19	35

The association between the height of the chylomicron curve and the total and neutral fat increment may be explained by assuming that the chylomicrons are composed of netural fat.

Though we found counts to parallel the neutral fat content of the serum in several curves, when all the results are taken together, it is seen that we have not found the close relationship suggested by Elkes, Frazer and Stewart (1939). Even in individual curves the peak of the neutral fat increment did not correspond with that of the chylomicron count in 21 out of 33 curves and the chylomicron peak occurred approximately as often after as before the neutral fat peak.

Occasionally low chylomicron counts were noticed with high neutral fat increments. This indicates that with absorbed fat as with the fasting serum fats the chylomicrons may represent only a variable fraction of the neutral fat. The remainder of the netural fat is invisible, but

is known to exist from the results of chemical analysis. If chylomicrons represent absorbed fat, as Frazer's and our own results suggest, then it is theoretically possible that a rise in chylomicrons during fat absorption might occur at the same time as a removal of invisible fat to the depots. In such a case the chylomicron count would be expected to rise, without any corresponding change in the neutral fat values ; and in point of fat this rise in chylomicrons with little or no change in the neutral fat values has been observed in three cases out of thirtyseven.

CHYLOMICRON COUNT IN SPRUE.

For the purpose of analysis the curves on sprue patients are grouped according to the height of the peak as follows :—

(1) Peak up to 50.
(2) Peak 51 to 100.
(3) Peak over 100.

The distribution of these types of curve is shown in Table VIII which gives the number of curves of each type in patients with and without liver therapy, and with and without diarrhoea at the time of the test. A separate table is given for the first curve done on each patient (table IX).

Many of the low curves were from patients having diarrhoea, but in the untreated cases of sprue the chylomicron curve is often low even when there is no diarrhoea.

Another common abnormality in the curves in sprue concerns the time of the peak. It is much more variable than in normal curves and frequently late. Curves with a peak value over 50 (groups 2 and 3) were distributed as follows according to the time of the peak :—

Time after giving meal.	..	2½	2½	3	3½	4	4½
No. of cases	..	5	20	15	16	6	2
					TOTAL	..	64

The average time of the peak was later than 3 hours in the sprue curves whereas it was 2½ hours in the normal curves.

The occurrence of low chylomicron curves in sprue has been shown not to be simply related to the degree of steatorrhoea. Table VIII suggests that there is, in cases without diarrhoea, an association between parenteral liver therapy and the occurrence of normal curves.

The changes in the chylomicron count associated with parenteral liver therapy were studied in four cases with an initially low chylomicron count and without diarrhoea. The results are presented in Table X. In each patient, a normal chylomicron count was found two or three weeks after beginning liver therapy (40 c.c. of concentrated extract followed, except in the first case, by 2 cc. daily). In three of the patients the proportion of the dietary fat which was being absorbed, as measured in four day periods, was known and the percentage of fat absorbed is shown in the last column of the table. In two of the patients the change in the chylomicron count was not associated with any improvement in fat absorption. In the third fat absorption had increased.

The curves done on patients not having liver have been grouped according to whether or not the patients were at the time gaining weight. Patients within ten pounds of their normal weight and those with diarrhoea are not included (Table XI). A low curve appears to be more common in the patients who are losing weight.

Thirty five of the chylomicron curves were done within a week of a blood sugar curve.

For purposes of comparison the chylomicrons curves are grouped into normal and abnormal according to whether the curve reaches a peak of 100 before 4 hours. The sugar curves are grouped according to whether there is an increment of more or less than 54mg. % before 1½ hours. Curves on patients with diarrhoea have been excluded.

The association between the groups of curves is shown in Table XII. About two thirds of the low chylomicron curves were associated with a sugar curve rising less than 34 mg. % and about two thirds of the normal chylomicron curves were associated with a sugar curve rising more than 34mg. %.

DISCUSSION :

The association between the height of the chylomicron curve and the blood glucose curve suggests that the chylomicron curve is a measure of general absorptive capacity. It has been shown that though the particles consist of fat, the curve is not a measure of total fat absorption so that the chylomicrons represent absorbed fat which is dealt differently from the greater part of absorbed fat. The analysis of the curves done concurrently with serum lipid estimations suggests that chylomicrons consist of absorbed neutral fat.

These conclusions are in accordance with Frazer's (1940) partition theory of fat absorption. He claims that fat is absorbed in two ways in the normal subject : as neutral fat, which has not undergone any splitting by lipase and is absorbed in particulate form, and as split fat absorbed after phosphorylation. The chylomicrons represent the unsplit fat absorbed without phosphorylation.

Frazer showed that in normal individuals an excess of lipase given with the fat meal produces a low chylomicron count. This he attributes to the fat being absorbed in the unsplit form. The results we obtained with calcium salts may possibly be interpreted as resulting from an activation of lipase. (Hawk and Bergheim 1942 p.329). If Frazer's theory is correct, a defect in the absorption of total fat, shown by steatorrhea, may be present in many cases of sprue in which normal absorption of unsplit fat is indicated by a normal chylomicron curve. Defective absorption of unsplit fat as shown by a low chylomicron curve, may occur particularly in the severe cases. Parenteral liver therapy corrects this abnormality, while total fat absorption is apparently often unaffected. The amount of fat normally absorbed without splitting is probably a small proportion of the whole (Bloor 1943 p.87) and when split fat is not being absorbed the correction of any impairment in the absorption of unsplit fat alone would not be reflected in any detectable improvement in total fat absorption.

The different reponse to parenteral liver therapy in the absorption of ununsplit and split fat suggests that a failure of different mechanisms is responsible for the deficiency in absorption of the two fractions in sprue. It appears that the fundamental deficiency is in the absorption of split fat, which may be due to a failure in phosphorylation (Stannus 1942). Less specific absorption defects, as of glucose and neutral fat, may be added later, in the more severe cases.

SUMMARY.

(1) A modified technique for the chylomicron count is described and the results of 18 curves done on normal subjects following the ingestion of a milk meal containing 18 gm. of fat are given.

(2) The curve was shown to vary with the amount of fat given, but in cases of sprue little relation was found between the degree of steatorrhea and the height of the curve. Low curves were obtained in normal subjects when the meal was given with calcium lactate but this substance did not produce steatorrhea, suggesting that chylomicrons only represent a part of absorbed fat.

(3) The relationship between 34 chylomicron curves and serum lipid curves done concurrently were analysed and it was concluded that chylomicrons represent part of the neutral fat in the serum.

(4) Eighty seven curves done on patients with sprue were analysed. Low curves were found with diarrhoea and frequently in patients who were

not gaining weight. With parenteral liver therapy patients whose curves had been low gave normal curves after two or three weeks.

(5) The results of the chylomicron curve and blood sugar curve were found to run parallel in about two thirds of the cases, suggesting that a flat chylomicron count occurs in the presence of a general defect of absorption.

(6) It is concluded that some of the fat is normally absorbed without splitting as neutral fat. Patients with sprue may fail to absorb neutral as well as split fat but these absorption defects are distinct and do not respond in the same way to treatment. Failure to absorb neutral fat is more common in the severe cases and responds to liver therapy.

FASTING SERUM LIPIDES AND FAT CURVES.

This section reports fat curves on a larger number of sprue patients than were available to Aldersberg and Sobotka (1943) and Barker and Rhoads (1937.) It includes 31 curves on 16 patients with tropical sprue, and 12 curves on 9 normal controls. Nearly all the sprue patients had two curves, either at different stages of the disease, or with and without substances added to the meal which might influence fat absorption.

MATERIAL AND METHODS

The normal controls were students and ambulant convalescent patients who had diseases not involving the gastro-intestinal tract. All the sprue patients had steatorrhoea and had lost weight ; anaemia and objective tongue signs where less common. They represent early cases of sprue acquired on wartime tropical service, the usual duration of symptoms being a few months. Although they differ in this respect from established sprue as seen in patients who have had longer periods in the tropics and then returned to temperate countries, there is no reason to suppose that there is any fundamental difference in fat absorption between early and later sprue. The sprue patients selected for fat curves represent 'severely ill' patients who had lost a lot of weight.

The general procedure was to take a fasting sample of 10 ml., and samples at $2\frac{1}{2}$, 3, $3\frac{1}{2}$ and 4 hours after a standard fatty meal. In the earlier curves, the timing of the after-samples was different, but experience showed that with the meal used the highest level of serum lipides lay between $2\frac{1}{2}$ and 4 hours, and the times given were then adhered to. The standard fatty meal consisted of evaporated milk, and contained 18 g. of milk fat. Most other workers have a mixed meal of much higher fat content, about 50 g. We have deviated from the accepted procedure for the following reasons :—

(1) Evaporated milk gives a homogeneous and accurately reproducible meal, so that it is possible to compare different curves in the same patient.

(2) The meal had to be tolerable even to the most severe cases of sprue ; even with the small dose of fat used, several of our patients had nausea, and they would certainly have vomited with a larger meal.

(3) Larger meals give a more prolonged rise in the blood fats, with a peak later than 4 hours in many cases ; with our meal, the maximum rise fell within a 4 hour period, and the test could be completed within 4 hours.

(4) All the patients studied were also on a fat balance, and it was desirable to give them a fat meal which was fairly close to the meal they would have had, so that only small adjustments in the fat intake for the rest of the day were required.

The standard fat meal was given by mouth, and not by duodenal tube, in spite of the known effect of fat delaying gastric emptying. It was found in preliminary experiments that fat given by duodeual tube produced a less

definite change in the chylomicron count and blood-fat level than did the same amount of fat given orally. This could be attributed to small intestinal hurry when a quantity of material is introduced into the duodenum. It is of interest that Peterson et al. (1942) found that sulphadiazine given by duodenal tube gave a smaller increase in blood level and urinary output than the same dose given orally.

Total fatty acids, lipide phosphorus, and total cholesterol were determined on a Bloor extract of 5 ml. of serum from each sample. For total fatty acids, the method of Stoddard and Drury (1929) was modified by the use of a Jena sintered glass crucible, porosity 4, in place of a Gooch crucible and filter pad, in filtering the fatty acid suspension. The final titration was done in a 15 ml. long-necked volumetric flask, to minimise absorption of Co_2. Lipide phosphorus was determined colorimetrically on ashed aliquots of Bloor extract. Total cholesterol was estimated by Sackett's method (King, 1945). Relative measurements of the opacity of the sera were made in a Klett-Summersen photo electric colorimeter ; and the chylomicron count was also done.

RESULTS.

The observed data in the tables are the total fatty acid in Eq/1., the lipide phosphruso in mg./100 ml., and the total cholesterol in mg./100 ml.

TABLE I.
SPRUE FASTING VALUES 26 CURVES).

q.		Mean	±S.D.	Coeff. var.
Total fatty acids mEq/L	..	11.95	±2.57	21.5 %
Phospholiqide F.A.	..	4.64	± .74	16 %
Cholesterol F.A.	..	3.10	± 0.6	19.4 %
Neutral F.A.	..	4.10	± 1.8	42 %
P/Total ratio.	..	0.397	±0.0557	14 %
Cholesterol/P	..	21.9	±4.15	19 %

NORMAL FASTING VALUES 12 CURVES.

Total F.A.	..	12.45	±2.47	19.8 %
Phospholipide F.A.	..	5.3	±0.73	13.8 %
Cholesterol F.A.	..	3.71	±0.54	14.6 %
Neutral F.A.	..	3.43	±1.63	47.5 %
P/Total ratio.	..	0.43	±0.04	9.3 %
Cholesterol.	..	21.8	±2.14	9.8 %

STANDARD DIFERENCE BETWEEN NORMAL AND SPRUE MEANS.

Total F.A.	..	0.87
Phospholipide F.A.	..	0.26
Cholesterol F.A.	..	0.19
Neutral F.A.	..	0·59
P/Total ratio	..	0·011

The values given for phospholipide fatty acid and cholesterol fatty acid are calculated on the same assumptions as were made by Peters and Manu (1943) in their extensive study of normal serum lipide values. The neutral fatty acid value represents the difference between the observed total fatty acid and the sum of the calculated values for fatty acids in phospholipide and cholesterol esters.

FASTING VALUES IN NORMALS AND SPRUE PATIENTS

Table I gives the mean values for the fasting serum lipides in 12 specimens from 9 normal subjects. The values are in good accord with the much larger normal series of Peters and Mann (1943). The sprue values given in the same table are derived from 26 specimens from 13 patients ; three patients who had received treatment have been excluded. The total fatty acids are on the average lower in sprue, but the difference is not significant on analysis. On the other hand, phospholipide and cholesterol fatty acids are both significantly lower in the sprue patients (P less than 0.02 and less than 0.01 respectively). The average level of calculated fatty acid in neutral fats is higher in the sprue patients, but the difference between it and our own small series of normals is not statistically significant ; it is significantly higher than the meal level in the normal series of Peters et al. (P less than 0.02).

The ratio of phospholipide fatty acid to total fatty acid is lower in the sprue patients, and the difference is significant (P less than 0.01). On the other hand, the ration of cholesterol to lipide phosphorus is the same as in normal subjects.

TABLE II A.

AVERAGE FAT INCREMENTS IN NORMAL SUBJECTS.

Subject		Total	Phospholipide	Chylo.	Neutral
1	..	4.27	0.52	0.36	3.39
II	..	2.20	0.44	0.16	1.60
II	..	0.50	—0.08	0.07	0.50
3	..	5.31	0.37	0	4.93
4	..	3.0	0.49	0.26	0.25
4	..	0.49	—0.21	0.16	0.54
5	..	1.70	0.24	0.01	1.45
6	..	0.63	0.34	0.18	0.12
7	..	1.64	—0.02	—0.13	1.79
8	..	0.5	—0.26	0	0.76
9	..	—0.07	—0.44	—0.1	0.51
Average	..	1.83	0.128	0.088	1.44

TABLE II B.

AVERAGE FAT INCREMENTS IN UNTREATED SPRUE.

Plain meal 13 curves.

Name	Total	P.L.	Chol.	Neutral
Cox	1.64	0.45	—1.22	2.14
Thomas ..	0.11	0.44	—0.21	—0.12
Shine ..	4.06	—0.20	0.02	4.24
McKean ..	0.29	—0.10	—0.26	0.65
Parkes ..	0.21	0.22	—0.24	—0.20
Collier ..	0.52	—0.07	0.04	0.56
Burton ..	0.61	—0.01	0.05	0.57
Parrot ..	0.43	0.02	—0.17	0.58
Sills	1.14	—0.58	—0.11	2.11
Oakes ..	0.24	0.49	—0.60	0.35
Kitchener ..	1.48	0.04	—0.06	1.50
Hyde ..	1.03	0.52	—0.03	0.54
Baker ..	0.13	—0.03	—0.35	0.52
Average ..	0.87	0.078	—0.262	1.12

CHANGES IN THE SERUM LIPIDES AFTER THE FAT MEAL.

This analysis of the changes after a fatty meal is based not on 'peak values', but on the average increment in three specimens taken between 2 hours and 4 hours after the meal. It will be seen from the curves that the time of the peak after taking the meal is variable even in normal subjects, and a good general picture of the change in the serum lipides cannot be based either on the highest recorded value, which may not be the true peak, or on a single fat estimation at a set time. The period 2-4 hours has been chosen because the highest recorded value for total fatty acids fell within that period in all the normal patients, and in all but two of the 31 curves on sprue patients. Both in sprue patients and in normals, the highest recorded value was usually at 3 or $3\frac{1}{2}$ hours.

TOTAL FATTY ACIDS.

Table II shows the change in total fatty acid, and in the various fractions, after the fat meal in eleven curves on nine normals, and thirteen curves on patients with sprue. From the sprue series, all curves in which glycerophosphate or lecithin was added to the meal, and all treated cases, have been excluded. Both in the normals and in the sprue series, the change in all the blood fat values after the same meal was very variable. One normal subject had a flat curve, and three others had an average increment of less than 1 mEq. per litre in total fatty acid. In the sprue series, one patient had no increase in total fatty acid, and seven others an average increase of less than 1 mEq./l. The average increase in total fatty acid in normals was about twice that in the sprue patients.

FATTY ACID FRACTIONS.

Increase in the serum phospholipides was much less constant than increase in the total fats, both in normals and in sprue patients ; five out of eleven normals showed a fall in the phospholipide fraction, and six out of thirteen sprues. One factor in bringing about the variation in the phospholipide response seems to be the fasting value ; on the whole, curves with high fasting values for phospholipide tended to show a drop in the phospholipide after the meal ; but this

negative correlation was not close. Since the fasting value for phospholipide was higher in normals than in 'sprue', there may have been some bias in the sprue patients in form of a phospholipide increase. In terms of averages, however, the sprue patients showed a lesser increase in phospholipide fatty acid than the normals, the increase in both cases being small in relation to the increase in total fatty acid.

In the normal subjects, the meal produced very little change in the serum cholesterol. Two patients showed a fall in serum cholesterol, and the others small increases, the average rise in fatty acids combined with cholesterol being only 0.088 mEq./l. All but three of the thirteen sprue patients showed a fall in serum cholesterol, and the average decrease in cholesterol fatty acids amounted to 0.262 mEq./l. As one would expect from the comparatively small changes in cholesterol and phospholipide fatty acids, the great part of the increase in serum fats after the meal was due to fatty acid in the form of neutral fat. This applied both to normals and sprue patients, but in the sprue patients the neutral fat increment was usually greater than the total fat increment, owing to the fall in cholesterol fatty acid and often in phospholipide fatty acid. While the average increment in total fatty acid in the sprue patients was only about half that in normals, the increment in neutral fatty acid was practically the same. Only two of the sprue patients failed to show an increase in neutral fatty acid.

In the noraml subjects, there was an increase in total fatty acids after the meal, a smaller and less constant increase in phospholipide fatty acid, little change in the cholesterol fatty acid, and an increase in neutral fatty acid sufficient to account for the greater part of the total increase in fatty acid. These changes are in general accord with the results of fat curves in normal people, as summarised by Bloor (1943). In the sprue patients, the increase in total fatty acid was less than in normals, phospholipide fatty acid was also less increased, cholesterol fatty acid showed a definite fall, and the increase in neutral fatty acid was not significantly different from that in normal subjects.

CURVES WITH GLYCEROPHOSPHATE, CHOLINE, AND LECITHIN.

Verzar and Laszt (1943) showed that the addition of glycerophosphate increased the absorption of fat from intestinal loops in the rat. Preliminary experiments showed that the addition of 10 g. of sodium glycerophosphate to our fatty meal increased the chylomicron count both in normal subjects and in sprue patients. Table III shows the results of paired fat curves, with and without 10 g. of sodium glycerophosphate, in one normal and six sprue patients. In the normal subject, the curve with glycerophosphate showed a greater increment in total fatty acid, mostly accounted for by an increased increment of neutral fatty acid. Of the sprue patients, three whose fat curve without glycerophosphate was low showed an increased with glycerophosphate, and two others (1 and 6) whose fat curve was fiarly normal also showed a small increase with glycerophosphate. Patient 3 differed from the others in that his apparent fat absorption without glycerophosphate was unusually high, and he showed a smaller increment in the glycerophosphate curve than in the 'control' curve. Glycerophosphate could not be said to have a constant effect on any individual fraction of the fat ; thus, there were increases in phospholipide increment in 4 curves and falls in 2 ; no very striking changes in cholesterol, except in one curve where a large decrease in cholesterol without glycerophosphate was absent in the glycerophosphate curve. Patients 2 and 5, who had shown a fall in neutral fatty acid in the curve without glycerophosphate, had increases in neutral fatty acid when glycerophosphate was given ; but the other four patients showed a smaller increment in neutral fatty acid in the glycerophosphate curve.

Aldersberg and Sobotka (1943) found that the addition of 10-15 g. of 20% commercial lecthin to a fat meal increased absorption in a small number of normals and sprue patients ; they used a single estimation of total blood fat

TABLE III

AVERAGE FAT INCREMENTS WITH AND WITHOUT 10 gm. SODIUM GLYCEROPHOSPHATE.

Subject	WITHOUT				WITH			
	Total fatty acid.	Phospholipide F.A.	Cholesterol F.A.	Neutral F.A.	Total fatty acid.	Phospholipide F.A.	Cholesterol F.A.	Neutral F.A.
1	1.46	0.54	—1.22	2.14	1.83	0.23	0	1.61
2	0.11	0.44	—0.21	—0.12	1.85	0.32	0.03	1.5
3	4.06	—0.20	0.02	4.24	0.66	0.24	—0.03	0.44
4	0.29	—0.10	—0.26	0.65	0.31	0.22	—0.13	0.22
5	—0.21	0.22	—0.24	—0.20	2.49	0.39	—0.07	2.16
6	1.14	—0.85	—0.11	2.11	1.58	—0.06	—0.29	1.93
Normal	1.70	0.24	0.01	1.45	3.13	0.31	0.03	2.79

TABLE IV

AVERAGE FAT INCREMENTS BEFORE AND AFTER TREATMENT WITH TCF.

Patient	BEFORE				AFTER			
	Total F.A.	Phospholipide F.A.	Cholesterol F.A.	Neutral F.A.	Total F.A.	Phospholipide F.A.	Cholesterol F.A.	Neutral F.A.
M	0.29	—0.10	—0.26	0.65	0.23	—0.17	—0.03	0.43
H	1.03	0.52	—0.03	0.54	0.80	0.29	—0.07	0.57
K	1.48	0.04	—0.06	1.50	—0.19	—0.16	—0.05	0.02
B	0.13	—0.03	—0.35	0.52	0.40	—0.40	—0.12	0.61

at 4 hours as their measure of fat absorption. In three curves done with and without lecithin, we used 10 g. of a preparation found on analysis to contain 50% phospholipide, so that our dosage was a little higher than the actual amount of lecithin given by Aldersberg and Sobotka. Of the three curves done with and without lecithin (Nos. 5, 7 and 8), two showed a smaller increase in the blood fats when lecithin was given, while the third had a larger increase in the blood fats in the lecithin curve ; but none of the patients showed the 50% increase described by Aldersberg and Sobotka. One patient, who had shown no increase in the fat curve with lecithin, showed a definite increase with sodium glycerophosphate. The dose of lecithin used was small in comparison with the dose of glycerophosphate, and it is possible that a larger dose of lecithin might have given a more definite response. Two curves done with 5 g. of choline afforded no evidence that choline increased fat absorption.

EFFECT OF LIVER TREATMENT.

Table IV shows fat increments on four patients with severe sprue before and after treatment with an Indian liver preparation, TCF. The dosage used was 4 ml. daily by intramuscular injection, and the preparation was clinically effective, all the patients showing general improvement and definite gain in weight. The figures show that this clinical improvement was not attended by any dramatic improvement in the fat curve, in fact three of the four patients showed a smaller increase in total fat. These results are superficially at variance with those of Barker and Rhoads (1937) who found that intensive liver treatment improved the blood fat curve ; but they used a much larger fat meal, and a different liver preparation in a dose of 10 ml. daily, so the two sets of results are not strictly comparable. TCF was the only liver preparation available to us in adequate amount. It has been shown to be effective in pernicious anaemia, and it was effective clinically in severe sprue, but it is not a 'crude' liver preparation, and it may not have contained the specific factor which improves fat absorption. Our lack of improvement in the fat curves was borne out by the failure of TCF to diminish the steatorrhoea appreciably.

DISCUSSION.

It is reasonable to suppose that increase in the blood fats after a fatty meal is mainly related to fat absorption. As a method of studying fat absorption however, the use of blood fat curves has limitations which must be kept in mind in any interpretation. In the first place, the change in blood fats is likely to reflect the rate at which fat is absorbed, rather than the total amount. Three of the normal subjects had negligible changes in the blood fat, yet none of them had steatorrhoea, so that their ultimate absorption of fat must have been satisfactory. In the sprue patients, too, there was no close correlation between the increment in blood fats, and the total fat absorption as determined by balance experiments. Even if fat is being absorbed at the same rate, the resulting change in the blood fats need not be the same, for fat is removed from the blood-stream into the liver and tissue depots in a quantity and at a rate which cannot be directly determined. The largest change in total fatty acid observed in our series was 5.3 mEq./l., and this could be accounted for by 10 g. of absorbed fat. Most of the increments even in normal subjects were much smaller, so it can be said that removal of fat from the blood occurs in considerable amount during the period of a fat curve, and the observed blood changes are only the resultant of absorbed fat, and fat removed to the liver and depots. A further complication is introduced by the possibility of lipide shifts between red cells and serum. Considereations of this nature serve to explain the great variability in fat curves observed by all workers. The curves reported here are equally variable, but although the ranges overlap widely, it can be said that in sprue patients the rise in serum lipides after a fatty meal is lower than in normals. This finding is in good accord with the more definite evidence of faulty

fat absorption which is given by stool analysis. It confirms earlier results done on a smaller number of patients (Barker and Rhoads, 1937 ; Aldersberg and Sobotka, 1943).

Comparison of the partition of the lipides before and after the meal is of interest in relation to the hypothesis put forward by Stannus (1942) to explain the mechanism of faulty absorption in sprue. Stannus accepted the 'partition theory' of fat absorption (Frazer, 1940), which claims that fat may be absorbed either as neutral fat in a fine emulsion, or as 'split fat', in which case phosphorylation may be an intermediate stage in absorption. Stannus suggested that in sprue the essential defect was in phosphorylation, and that the absorption defect would concern only split fats and cholesterol, but would not affect the absorption of unsplit fat. Those of our results which are in harmony with Stannus' hypothesis can be summarised as follows :—

(1) The fasting values for cholesterol and lipide phosphorus are significantly lower in sprue patients than in normal subjects ; the fsating values for neutral fat are normal or even increased in sprue.

(2) After a fatty meal, the average increase in all lipide fractions is smaller in sprue patients than in normal subjects ; but the neutral fat increment in sprue is 80% of the normal average, whereas the phospholipide increment is only 60 % of the normal average. The fact that an increase in phospholipides occurs in about half the cases of sprue does not necessarily mean that they are absorbing fat in that form, for phosphorylation of fats occurs in the liver, and Reinhardt et al (1944) have shown that phospholipide found in the liver can enter the blood-stream, whereas phospholipide formed in the intestine is not available to the blood plasma. On the other hand, the results of blood analysis cannot exclude the theroetical possibility of fat being absorbed as phospholipide, and reconverted to neutral fat in the intestinal wall before entering the chyle. Two of the sprue patients showed a fall in the neutral fatty acid after the fat meal. This might be caused by unusually rapid withdrawal of fat into the depots ; but it is also possible that some cases of sprue may have impaired absorption even of neutral fat, as a secondary phenomenon comparable to the general absorption failure which is found in chronic starvation.

(3) Normal subjects show a negligible change in the serum cholesterol after the fatty meal, in spite of the fact that a fatty meal stimulates an outpouring of bile. In the sprue patients, the fatty meal is followed by a decrease in the serum cholesterol, which can best be explained by a failure to reabsorb the cholesterol poured out with the bile.

(4) The fact that glycerophosphate improved the rate of fat absorption in five out of six sprue patients is consistent with its having improved phosphorylation ; although the way in which it would do so remains obscure. We failed to observe an improvement in fat absorption with lecithin, but such an improvement has been observed by Adlersberg and Sobotka (1943). Our negative results with choline suggest that lecithin, if active, might owe its activity to its glycerophosphate content, and it is possible that larger doses of lecithin might be more uniformly effective.

The limitations of blood fat curves as a measure of absorption are such that these observations cannot be taken as a pfoof of the Stannus hypothesis ; but they lend themselves more readily to explanation on his basis than on any other at present available.

SUMMARY

Total fatty acid, lipide phosphorus and cholesterol were essimated in the serum of 16 patients with tropical sprue, and 9 normal controls. These estimations were repeated at intervals after a standard meal containing 18 g. of fat ; in this way, 12 fat curves were done on the normal controls, and 31 on the patients with sprue.

It was found that the fasting level of total fatty acid in sprue did not differ

significantly from normal values ; but phosphllipide and cholesterol were significantly lower, while the calculated value for neutral fatty acid was higher than normal. After the fatty meal, the total fatty acids in the sprue patients increased less than in normal subjects ; phospholipides showed a smaller increase than neutral fatty acid. The cholesterol, which was little affected by the meal in normal controls, usually fell in the sprue patients. Sodium glycerophosphate, in a dose of 10 g., raised the height of the fat curve in five out of six patients with sprue ; a similar effect was not found with choline or lecithin. No significant change was demonstrated in the fat curve after a period of liver treatment in 5 patients.

Although the results of serial fat estimations in serum are no doubt affected by metabolic changes not directly concerned with fat absorption, the low fat curve in sprue fits in well with the more direct evidence of faulty fat absorption given by stool analysis. The changes in the different fractions of serum lipides are discussed in relation to Stannus' hypothesis that the absorption defect affects only those lipides which are phosphorylated during absorption. The observed results can be well explained on the basis of this hypothesis, but they cannot be said to contribute directly to proving it.

RESULTS OF BLOOD FAT CURVES IN NORMALS AND SPRUE PATIENTS.

The first five columns represent direct observations ; the remaining three columns are calculated on assumptions described in the text. The figures for Chylomicron count represents the acutal count in a standard field ; that for opacity is the reading on a Klett-Summersen photo- electric colorimeter with a red filter.

Curves on Normals with oral meal.

	Time in hours	Chylomicron count.	Opacity.	Total fatty acid. (mEq/L)	Lipid phosphorus (mg=100ml.)	Total Cholesterol (mg/100ml.)	Phospholipide fatty acid. (mEq(L)	Cholesterol acid. (mEq/L)	Neutral acid (mEq/L)
1.	0	2	..	10.75	8.0	146	4.64	2.73	3.38
	2	128	..	16.85	8.6	154	4.98	2.88	8.99
	3	90	..	15.62	9.7	158	5.62	2.95	7.05
	4	33	..	12.58	8.4	184	4.87	3.44	4.27
	5	10	..	12.05	8.5	133	4.93	2.48	4.64
2.	0	3	29	10.55	7.5	159	4.35	2.98	3.22
	2	125	80	12.19	8.45	169	4.90	3.16	4.13
	3	115	112	13.23	7.8	164	4.53	3.07	5.63
	4	70	73	12.83	8.5	172	4.93	3.20	4.70
	5	60	48	11.63	6.4	158	3.71	2.96	4.96
3.	0	1	35	13.45	9.25	182	5.37	3.40	4.68
	2	20	43	13.45	9.25	195	5.37	3.64	4.44
	$2\frac{1}{2}$	20	43	13.45	9.3	195	5.39	3.64	4.42
	3	100	55	13.67	8.75	190	5.08	3.55	4.04
	4	40	74	14.70	8.65	186	5.02	3.48	6.20
4.	0	15	32	10.89	8.5	194	4.93	3.63	3.33
	2	185	89	11.66	8.7	194	5.04	3.63	2.99
	$2\frac{1}{2}$	140	93	11.98	8.7	187	5.04	3.50	3.44
	3	105	79	12.87	8.45	187	4.91	3.50	4.46
	4	20	79	12.74	8.25	187	4.78	3.50	4.46
5.	0	..	..	10.96	9.45	189	5.48	3.53	1.95
	2	..	61	11.22	6.75	198	5.07	3.70	2.45
	$2\frac{1}{2}$	..	68	11.76	10.9	198	6.32	3.70	1.74
	3	..	51	11.83	8.5	198	4.93	3.70	3.20
	4	..	29	11.18	10.7	199	6.20	3.72	1.26

CURVES ON SPRUE WITH AND WITHOUT GLYCEROPHOSPHATES.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
4. Without								
0	0	34	7.27	7.0	135	4.06	2.53	0.66
2	5	37	7.27	6.35	119	3.68	2.23	1.36
3	25	54	7.71	7.25	121	4.21	2.26	1.24
4	10	52	7.71	6.9	124	4.0	2.32	1.39
5	5	36	8.07	6.5	124	3.77	2.32	1.98
4. With								
0	10	31	7.27	6.2	128	3.59	2.40	1.28
2	10	36	7.27	6.65	119	3.85	2.23	1.19
3	25	40	7.6	6.25	199	3.62	2.23	1.75
4	50	47	7.88	6.85	126	3.97	2.36	1.55
5	15	37	7.60	6.75	126	3.91	2.36	1.33
5. Without								
0	80	..	15.08	10.4	196	6.04	3.66	5.38
2½	140	..	15.85	9.8	188	5.68	3.51	6.66
3	220	..	15.85	9.1	188	5.27	3.51	7.07
3½	200	..	16.52	8.95	191	5.19	3.57	7.66
4	80	..	16.30	8.8	191	5.10	3.57	7.63
5. With								
0	40	..	12.23	8.2	193	4.76	3·61	3.86
2½	80	..	15.52	7.9	180	4.58	3.36	4.58
3	90	..	13.06	8.1	177	4.70	3.31	5.05
3½	425	..	14.22	8.1	181	4.70	3·38	6.14
4	80	..	14.15	8.1	175	4.70	3.27	6.18

CURMES ON SPRUE WITH AND WITHOUT GLYCEROPHOSPHATES.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
2. Without								
0	5	30	11.19	7.6	132	4.41	2.45	5.33
2	125	91	11.42	7.7	121	4.47	2.25	5.70
3	50	69	11.19	8.5	115	4.93	2.15	4.11
4	110	84	11.29	8.9	124	5.16	2.32	3.81
5	55	57	12.55	9.1	124	5.28	2.32	4.95
2. With								
0	28	17	12.0	7.45	157	4.32	2.94	4.74
2	95	51	13.21	8.4	176	4.87	3.29	5.05
3	185	111	14.10	8.0	155	4.64	2.90	5.56
4	140	102	14.35	7.6	146	4.41	2.73	7.21
5	50	44	13.57	7.8	149	4.53	2.79	6.25
3. Without								
0	10	54	12.34	9.4	154	5.46	2.88	4.0
$2\frac{1}{2}$	230	188	16.46	8.7	157	5.04	2.94	8.48
3	250	184	16.51	8.95	155	5.19	2.90	8.42
$3\frac{1}{2}$	160	158	16.15	9.1	155	5.27	2.90	7.98
4	50	162	16.55	9.2	155	5.33	2.90	8.32
3. With								
0	78	124	13.60	7.95	163	4.61	3.04	5.95
$2\frac{1}{2}$	120	124	15.18	9.1	170	5.28	3.18	6.72
3	165	124	14.22	8.3	157	4.82	2.94	6.46
$3\frac{1}{2}$	155	106	13.38	7.7	157	4.46	2.94	5.98
4	135	93	14.03	8.6	164	4.98	3.06	5.99

Normals—with and without glycerophosphate.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol total (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
8. Without								
0	6	35	11.62	8.3	186	4.82	3.48	3.32
2	30	52	11.62	8.4	186	4.87	3.48	3.27
2½	165	75	12.70	8.7	187	5.04	3.50	4.16
3	60	84	12.78	8.7	186	5.04	3.48	4.26
4	15	48	14.47	8.8	186	5.10	3.48	5.89
With								
0	5	32	13.38	9.1	208	5.28	3,89	4.21
2	150	107	14.82	9.45	208	5.49	3.89	5.44
2½	230	174	15.98	9.8	212	5.68	3.97	6.33
3	140	159	16.60	9.85	208	5.72	3.89	6.99
4	30	94	16.90	8.25	208	5.37	3.89	7.69

Curves on Sprue with and without glycerophosphates.

1. Without								
0	20	..	9.34	6.6	220	3.82	4.12	1,40
2	140	..	11.43	7.35	150	4.27	2.80	4.36
3	175	..	11.32	7.6	145	4.41	2.71	4.20
4	135	..	9.66	7.6	170	4.41	3.18	2,07
5	..	..	10.09	7.35	145	4.27	2.71	3,11
1. With								
0	15	..	11.72	7.9	208	4.58	3.89	3.25
2	185	..	12.51	8.1	208	4.69	3.89	3.93
3	90	..	14.03	8.1	208	4.69	3.89	5.43
4	80	..	14.11	8.7	208	5.04	3.89	5.18
5	15	..	12.34	7.5	210	4.34	3.92	4.08

CURVES ON NORMALS WITH ORAL MEAL.

Time in hours.		Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Total Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
6.	0	3	..	14.60	10.0	220	5.8	4.12	4.68
	1	5	..	14.74	11.5	220	6.67	4.12	3.95
	2	50	..	16.05	11.5	220	6.67	4.12	5.26
	3	70	..	22.62	10.4	220	6.04	4.12	12.46
	4	50	..	21.05	10.0	220	5.8	4.12	11.13
7.	0	..	..	12.15	10.1	214	5.86	4.0	2.29
	$2\frac{1}{2}$	..	..	12.40	9.45	214	5.48	4.0	2.92
	3	..	..	12.70	9.5	214	5.52	4.0	3.18
	$3\frac{1}{2}$	..	..	12.15	9.5	214	5.52	4.0	2.63
	4	..	..	13.10	9.95	214	5.77	4.0	3.33
8.	0	..	..	18.85	11.55	254	6.70	4.75	7.4
	$2\frac{1}{2}$	..	..	18.15	10.65	250	6.18	4.67	7.3
	3	..	..	18.70	10.85	250	6.29	4.67	7.74
	$3\frac{1}{2}$	..	..	19.10	10.95	250	6.36	4.67	8.07
	4	..	..	18.55	10.4	246	6.04	4.60	7.91

CURVES ON NORMALS WITH DUODENAL—TUBE MEAL

2.	0	3	..	8.92	7.3	200	4.23	3.74	0.95
	2	20	..	9.46	7.3	200	4.23	3.74	1.49
	3	15	..	9.46	7.3	211	4.23	3.94	1.29
	4	10	..	9.32	6.9	200	4.0	3.74	1.58
	5	10	..	9.25	6.9	200	4.0	3.74	1.51

The numbers correspond to those already given as "normal curves". i.e. without duodenal tube, but with the same meal.

2.	0	5	..	13.31	10.6	236	6.15	4.42	2.74
	2	10	..	13.31	10.8	250	6.27	4.68	2.36
	3	20	..	14.25	11.45	250	6.64	4.68	2.93
	4	40	..	15.37	12.1	250	7.02	4.68	3.67
	5	30	..	13,60	11.8	236	6.84	4.42	2.34

CURVES ON SPRUE WITH AND WITHOUT GLYCEROPHOSPHATES.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
6. Without								
0	5	..	16.51	7.9	191	4.58	3.57	8.36
2½	30	..	15.36	7.6	177	4.41	3.31	7.64
3	85	..	15.48	7.9	172	4.58	3.22	7.68
3½	60	..	17.02	8.35	185	4.84	3.46	8.72
4	50	..	16.82	8.6	177	4.99	3.31	8.52
6. With								
0	10	..	14.11	8.4	202	4.87	3.78	5.46
2½	150	..	16.49	9.3	202	5.40	3.78	7.31
3	125	..	16.60	8.55	191	4.96	3.57	8.07
3½	150	..	16.70	9.35	202	5.43	3.78	7.49
4	50	..	15.63	8.6	193	4.99	3.61	7.03

CURVES ON SPRUE WITH LECITHIN AND CHOLINE.

7. Without								
0	8	..	8.25	6.3	119	3.65	2.22	2.38
2½	20	..	8.25	6.3	114	3.65	2.13	2.47
3	10	..	8.82	6.3	123	3.65	2.30	2.87
3½	5	..	8.82	6.1	119	3.54	2.22	3.06
4	5	..	8.68	6.1	121	3.54	2.26	2.88
7. With 5 g. choline								
0	3	..	8.11	6.55	124	3.80	2.32	1.99
2½	40	..	7.78	5.75	117	3.34	2.19	2.25
3	50	..	7.96	6.1	113	3.54	2.11	2.31
3½	50	..	7.96	6.2	117	3.60	2.19	2.17
4	20	..	7.96	6.2	119	3.60	2.22	2.14

CURVES ON SPRUE WITH LECITHIN AND CHOLINE.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
8. With Choline								
0	58	..	12.38	8.35	175	4.84	3.28	4.26
2½	46	..	12.63	7.95	178	4.61	3.33	4.69
3	65	..	13.17	8.55	178	4.96	3.33	4.88
3½	43	..	13.17	8.50	178	4.93	3.33	4.91
4	44	..	12.30	8.10	178	4.70	3.33	4.27
8. With lecithin								
0	50	..	11.43	8.4	174	4.87	3.26	3.30
2½	97	..	11.43	8.4	168	4.87	3.15	3.41
3	83	..	11.22	8.4	171	4.87	3.20	3.15
3½	98	..	11.57	8.6	171	4.99	3.20	3.38
4	70	..	11.57	8.5	174	4.93	3.26	3.38
9. Without								
0	15	..	13.61	9.0	191	5.32	3.57	
2½	70	..	14.47	9.0	180	5.32	3.37	5.78
3	83	..	13.83	9.05	183	5.35	3.42	5.06
3½	145	..	13.83	9.05	183	5.35	3.42	5.06
4	80	..	13.61	9.05	183	5.35	3.42	4.84
9. With lecithin								
0	5	..	13.50	8.65	184	5.20	3.44	5.04
2½	40	..	13.83	8.65	184	5.02	3.44	5.37
3	58	..	15.32	9.95	185	5.19	3.46	6.67
3½	133	..	15.02	8.75	184	5.08	3.44	6 50
4	85	..	15.13	8.75	184	5.08	3.44	6.61

CURVES ON SPURE WITH LECITHIN AND CHOLINE.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
5. With leithin								
0	20	..	17.18	10.7	204	6.20	3.82	7.16
2½	195	..	17.18	10.7	199	6.20	3.72	7.26
3½	90	..	16.89	10.3	199	5.97	3.72	7.20
3½	177	..	16.52	10.3	199	5.97	3.72	6.83
4	205	..	16.33	9.7	199	5.62	3.72	6.99

CURVES ON SPRUE BEFORE AND AFTER LIVER TREATMENT

10. Before treatment								
0	5	50	13.41	7.35	164	4.26	3.07	6.08
2½	60	77	13.96	7.05	158	4.08	2.98	6.9
3	45	98	15.84	7.2	164	4.18	3.07	8.59
3½	110	97	13.98	8.05	158	4.67	2.98	6.25
4	80	100	14.93	7.0	158	4.06	2.98	7.89
10. After treatment								
0	45	..	13.73	8.6	163	4.98	3.05	5.70
2½	15	..	13.80	7.75	159	4.49	2.98	6.33
3	70	..	13.01	8.25	159	4.78	2.98	6.25
3½	120	..	13.80	8.45	159	4.91	2.98	5.91
4	60	..	13.80	8.25	162	4.78	3.03	5.99
11. Before treatment								
0	5	22	11.09	6.85	177	3.97	3.31	3.81
2½	80	79	11.63	7.4	170	4.29	3.18	4.16
3	70	78	12.24	7.65	174	4.44	3.26	4.54
3½	100	70	11.84	7.75	176	4.49	3.29	4.06
4	...	76	12.28	7.8	176	4.53	3.29	4.46

CURVES ON SPURE BEFORE AND AFTER LIVER TREATMENT.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Total Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
11. After liver treatment								
0	2	..	10.71	7.75	164	4.49	3.07	3.15
2½	63	..	11.48	7.85	160	4.56	2.99	3.93
3	80	..	11.48	7.95	160	4.62	2.99	3.87
3½	30	..	11.48	8.3	162	4.82	3.03	3.63
4	25	..	11.57	8.45	162	4.91	3.03	3.63
12. Before liver treatment								
0	5	..	10.74	6.5	131	3.77	2.45	4.52
2½	100	..	10.74	6.55	113	3.80	2.11	4.63
3	105	..	11.08	6.3	116	3.66	2.17	5.25
3½	140	..	11.08	6.5	111	3.77	2.08	5.23
4	100	..	10.42	6.55	109	3.80	2.04	4.58
12. After liver treatment								
0	10	..	11.12	6.7	125	3.88	2.34	4.90
2½	35	..	11.25	6.45	125	3.74	2.34	5.17
3	45	..	11.30	6.5	118	3.77	2.21	5.32
3½	40	..	11.48	6.5	118	3.77	2.21	5.50
4	40	..	11.79	6.6	120	3.83	2.25	5.71
4. After Liver treatment								
0	15	..	12.49	7.85	186	4.55	3.48	4.46
2	60	..	12.62	7.65	187	4.44	3.50	4.68
3	125	..	13.03	7.40	180	4.29	3.37	5.37
4	75	..	12.52	7.60	186	4.41	3.48	4.63
5	20	..	12.52	7.75	178	4.49	3.33	4.70

MISCELLANEOUS SPRUE CURVES

2. After nicotinic acid plus riboflavine								
F	8	33	10.43	8.05	177	4.67	3.32	2.44
2½	35	49	10.63	8.1	169	4.70	3.16	2.77
3	50	49	10.39	7.75	169	4.49	3.16	2.74
3½	20	37	9.92	7.6	170	4.41	3.18	2.33
4	20	44	9.92	8.25	172	4.78	3.22	1.92

MISCELLANEOUS SPURE CURVES.

Time in hours.	Chylomicron count.	Opacity	Total fatty acid. (mEq/L)	Lipide Phosphorous (mg/100ml)	Total Cholesterol (mg/100ml)	Phospholipide fatty acid (mEq/L)	Cholesterol fatty acid. (mEq/L)	Neutral fatty acid (mEq/L)
13. After full treatment								
F	4	30	11.75	6.2	153	3.59	2.86	5.30
2	75	97	13.90	7.95	148	4.62	2.77	6.51
3	120	95	14.16	5.7	148	3.30	2.77	8.09
4	80	49	13.28	4.9	147	2.84	2.75	7.69
5	60	44	12.58	4.9	147	2.84	2.75	6.99
14. No treatment								
F	12	..	9.47	6.3	216	3.65	4.04	1.78
2	35	..	8.78	7.2	181	4.18	3.38	1.22
3	32	..	10.21	7.2	196	4.18	3.67	2.36
4	34	..	9.76	7.2	182	4.18	3.38	2.20
5	..	..	9.15	7.0	174	4.06	3.26	1.83
15. After Liver treatment								
F	7	47	22.07	11.6	216	6.74	4.04	11.29
2½	60	97	22.25	12.0	212	6.96	3.97	11.62
3	75	82	22.42	12.6	206	7.32	3.86	11.24
3½	125	70	23.73	12.5	214	7.26	4.00	12.47
4	40	70	23.01	12.5	220	7.26	4.12	11.63
16. After Liver treatment								
F	1	32	9.49	5.8	116	3.36	2.17	3.96
2½	45	36	9.63	5.4	118	3.13	2.20	4.30
3	55	45	11.32	5.5	118	3.19	2.20	5.93
3½	35	33	10.13	5.7	113	3.31	2.11	4.71
4	46	45	..	5.5	113	3.19	2.11	..

ADDITIONAL FASTING VALUES

Patient No.								
6	10	..	14.32	10.1	199	5.86	3.72	4.74
8	15	..	10.71	8.0	154	4.64	2.88	3.19
9	8	..	13.71	9.65	197	5.60	3.69	4.42
15	20	..	30.75	15.2	233	8.81	4.36	17.58
15	..	..	26.20	14.9	236	8.64	4.42	13.14

ABSORPTION OF NON-FATTY SUBSTANCES.

Although the chief object of the biochemical investigation was to obtain data on fat absorption in an adequate number of early cases of sprue, we have made a certain number of observations on the absorption of substances other than fats. Most of this material concerns the absorption of glucose, as judged by the glucose tolerance test; but a few observations are included on the absorption of iron, amino-acids, and iodides, and some information bearing on absorption has also been obtained from nitrogen and electroyte balances.

BLOOD SUGAR CURVES.

It is generally recognised that a flat type of blood sugar curve is common, though not universal, in sprue patients after a glucose meal. This flat curve is caused by impaired absorption of glucose, rather than by any alteration in carbohydrate metabolism, since intravenous injection of glucose gives a normal or even a high blood-sugar curve (Fairley, 1936). We have therefore had as our main object not the accumulation of further data on glucose absorption itself, but an assessment of whether there was any relationship between the glucose and the fat absorption defects. Our material for this purpose consists of 70 curves done on 27 patients with sprue; specimens were taken at half-hourly intervals up to 2 hours after giving 50 g. glucose, and we have based our analysis of the results on the difference between the fasting values and the highest observed blood-sugar figure within one hour of the meal. Peaks of blood-sugar occurring later than 1 hour have not been included, since they are in themselves an abnormality. Such peaks were observed in nine out of 25 untreated patients.

Table I shows the mean fasting values of blood sugar in 15 untreated patients and in 15 patients who had received treatment with parenteral liver; the fasting value is significantly lower in the untreated group (P less than 0.02). Serial observations on individual cases showed that increase in the fasting value of blood sugar occurred within 2 weeks of beginning liver therapy. The low fasting blood sugar level in untreated sprue is probably analogous to that found in starvation, and is brought about either by actual restriction of the carbohydrate in the diet, or by failure to absorb part of the dietary carbohydrate.

TABLE I.

Fasting blood sugar in untreated sprue, and after parenteral liver treatment.

	Untreated (15 cases)	Treated (Parenteral liver) 15 cases.
Mean.	85-8 mg./100 ml.	94-5 mg./100 ml.
S.D.	+10.2 „	7.5 „
Range.	71-100 „	83-111 „
Difference of means	8.7	
Standard error or difference.	3.27	

TABLE II

Frequency distribution of 25 untreated cases of sprue with reference to the maximal blood-sugar increment after 50 g. glucose.

	Blood Sugar Increment (mg./100 ml.) Less than				
Number of cases	20 6	20-30 4	30-40 6	40-50 3	Over 50 6

TABLE III.

Correlation table of percentage fat absorption, and maximum blood-sugar increment after 50 g. glucose.

	Percentage Fat Absorption (%)			
	Less than	70-80	80-90	Total
Less than 30	4	3	6	13
Blood-sugar 30-40 increment mg./100 ml.)	2	5	6	13
greater than 40	4	5	6	15
Total :	10	13	18	41

The distribution of the maximum blood-sugar increment in the first hour in 25 untreated patients with sprue is shown in Table II. Sixteen of the patients had a rise in the blood-sugar of less than 40 mg./100 ml., and ten of these had less than 30 mg./100 ml., On the other hand, six patients had curves which would be generally accepted as 'normal'. The incidence of 'normal' and 'low' curves was found to be quite unrelated to the degree of the fat absorption defect, as judged by fat balance experiment. Table III gives the figures on which this statement is based. It will be seen that 'normal' sugar curves may be found in patients with a severe fat absorption defect, while other patients with a mild fat absorption defect may have a low blood-sugar curve. Three patients (not included in the Table) whose fat absorption had improved with treatment to normal levels (over 90%) were all found to have normal blood-sugar curves. In interpreting these results it must be borne in mind that fat balance measures total fat absorption, whereas a glucose tolerance curve measures only the rate of sugar absorption. Although the incidence of definitely abnormal sugar curves is less than that of steatorrhoea, it is quite possible that the glucose absorption defect appears concurrently with the fat absorption defect, but that it cannot be detected by the tolerance curve method. In this connection, it may be pointed out that fat curves of normal type can be obtained in patients whose impaired fat absorption is well attested by heavy steatorrhoea.

We have also made a limited number of observations on the absorption of simple water-soluble substances. Although glucose is also water-soluble, there is strong evidence of the existence of a special phosphorylation mechanism for its absorption, and it seemed important to find out whether in the early stages of sprue the absorption defect was limited to fat and glucose, or whether there was a general impairment of absorption. Most of our own observations were made on iron absorption, using serum iron curves.

SERUM IRON.

Table IV shows the serum iron values in six patients at 2, 3 and 4 hours after a dose of 7½ grains ferrous sulphate, compared with the fasting value. The percentage fat absorption and the maximum blood-sugar increment after 50 g. glucose are also shown. All the curves showed an increase in the serum iron of 100/100 ml. or more, except the first curve on patient 6 who had an almost flat curve ; after three weeks of parenteral liver therapy, this patient's serum iron rose 109 x/100 ml., after iron, and concurrently his blood sugar curve rose to within normal limits, and his fat aasorption improved. Comparison with blood sugar curves and fat absorption figures in the other patients showed that there could be a good rise in the serum iron curve when fat absorption is poor, and also when the blood sugar curve is abnormally low.

We have also tested the absorption of iodide in eight patients, by determining the time taken for iodide to appear in the saliva after the ingestion of 3 grains of sodium iodide ; the times ranged from 5 to 27 minutes, all within the normal range. Dixon (1946) found that the blood amino-acid rose in the normal way after the ingestion of 25 g. of glycine by 4 convalescent sprue patients ; we have made a similar observation in one patient with definite early sprue. Thaysen (1932) found that in most cases of idiopathic steatorrhoea the faecal nitrogen was within normal limits ; in one of his nine patients there was an abnormally large loss of nitrogen in the faeces. He concludes that in general protein absorption is not imparied in sprue. We have found in our observation on electrolyte changes in sprue (see later section) that formed sprue stools contain

TABLE IV

SERUM IRON CURVES, WITH BLOOD SUGAR INCREMENT AND %FAT ABSORPTION.

	Serum iron (/100 ml)				Blood sugar increment	% Fat absorption.
Patient	Fasting	2 hr.	3 hr.	4 hr.	(mg/100 ml)	
1	93	83	297	137	45	63
2	102	230	..	143	42	81
3	113	237	283	230	20	85
4	94	286	450	462	37	78
5	90	..	..	232	38	70
6	100	115	110	127	23	56
7 (after liver)	166	242	252	275	49	74

no excess of chloride ; their content of sodium is rather high, but that is more likely to be due to soap formation than to any defect in sodium absorption. On the other hand, in phases of watery diarrhoea the stools contain large amounts of sodium and chloride, and raising the salt content of the diet increases the loss of sodium and chloride in the stools.

In general, it may be said that we have found no evidence of a generalised absorption defect in the majority of cases of sprue, including some with heavy steatorrhoea and a flat glucose tolerance curve. Exceptional cases do show imparied absorption of substances other than fat and glucose, and this is especially so when watery diarrhoea is present.

NITROGEN METABOLISM IN SPRUE. SECTION II

INTRODUCTION.

The literature on sprue has up to the present dealt mainly with fat and carbohydrate metabolism in this disease. It therefore seemed important that as thorough a study as possible should be made of the metabolism of "Nitrogen" (otherwise protein). This importance becomes greater when it is considered that fat and carbohydrate, either or both play mainly the role of an energy source ; whereas that played by protein is largely structural or functional. Therefore any gross error in protein metabolism is of considerable pathological significance.

A study of this type falls under two headings :—

(a) Absorption.

Examination of faecal nitrogen in relation to dietary nitrogen to ascertain the degree of absorption.

(b) Utilisation.

Examination of urinary nitrogen and its correlation with absorbed nitrogen thus showing whether a state of negative or positive balance exists.

All the patients studied were in remission phase of the disease except one who was studied in relapse and remission.

EXPERIMENTAL.

I. Diet.

Diets used were as follows :—

Proteins { A. 140-160 gr. B.

Fat : A. 90-96 Gr. B. 66-69 Gr.

Carbohydrate : A. 250 B. 215

Values for protein content of foods were taken from McCance and Widdowson-'Chemical Composition of Foodstuffs.'

The protein fraction of these diets was "high grade" consisting of meat, fish, eggs and milk.

A difficulty encountered was the capricious nature of the sprue appetite, tending to variations in the day to day intake and also variations between the average intake of different patients.

II. SPECIMEN COLLECTION.

(a) Urine.

Urinary output was collected and measured over three or four-day periods. After micturation the urine was transferred to ghee tins and preserved under a layer of kerosene. The classical fixation with mineral acid was not practicable owing to the shortage of A.R. quality acid. However, a check made with urine preserved with kerosene and urine fixed with 10% W/V H_2SO_4 showed the ammonia loss to be within the biological error of these experiments.

(b) Faeces.

The periods of collection were similar to those of urine (three or four-day) ; stools after passage were transferred to tin pans, and formalised to inhibit bacterial action.

III. NITROGEN ESTIMATION.

(a) Urine.

The volume of the composite sample was measured and the whole well mixed. 2 ml. was removed and digested with 5 ml. (conc. H_2SO_4 plus 2% sodium selenite).

The digest was made to a volume 50 ml. and nitrogen estimation made on 10 ml. of the final solution. The micro-kjeldahl method was used employing N/50 Acid and back titrated with N/100 NaOH using methyl red as indicator.

(b) Faeces.

The pooled specimens of faeces were thoroughly mixed and mascerated to obtain homogenity. A 10 gr. sample was accurately weighed and mixed thoroughly with 12 ml. of water. 10 ml. conc H_2SO_4 was slowly added with stirring and the whole brought to the boil. By this method, a dark brown homogeneous mixture was obtained. The mixture was diluted to 100 ml. and 10 ml. digested in the same manner as for urine. The digest was diluted to a volume of 50 ml. and a micro-kheldahl estimation made on 10 ml. of the solution.

RESULTS.

These are tabulated in Tables I and II. In view of the biological error, results are only expressed to the first decimal place.

TABLE I.

Average per diem.

Case.	Exprt. No.	Period (days)	Faecal wt.	Faecal N_2	% Faecal wt.	Diet N_2
1	1	12	153	2.2	1.5	23
	2	12	130	1.6	1.2	20
2	3	12	178	2.5	1.3	24
	4	12	186	2.2	1.2	24
3	5	12	85	1.3	1.4	19
4	6	12	187	2.0	1.1	22
5	7	14	547	4.0	.8	23
	8	12	315	3.6	1.2	23
	9	12	287	2.9	1.0	22
6	10	12	140	1.3	.9	25
	11	12	240	3.0	1.2	23
7	12	12	223	2.4	1.1	20
	13	12	282	2.6	.0	20
	14	12	315	2.3	.7	18
8	15	12	99	1.0	1.0	22
	16	8	153	1.8	1.2	18
9	17	12	133	1.1	.8	25
	18	12	147	1.6	1.1	26
10	19	11	144	1.3	.9	15
	20	12	130	·6	.46	12

TABLE II

Expressed as average per 24 hours.

Case	Exprt. No.	Period (days)	Faecal N_2 Gr.	Urinary N_2 Gr.	Dietary N_2 Gr.	Nitrogen retention gr
1	1	11	1.2	8.0	15.8	6.6
..	2	12	0.6	6.7	11.5	4.2
..	3	12	1.6	8.5	16	5.9
2	4	12	2.4	9.0	19.16	8.2
..	5	12	2.6	11.2	18	4.2
..	6	12	2.3	8.8	19.5	8.4
3	7	14	4.0	16.5	23.5	3.0
..	8	12	3.6	20.8	23.3	−1.1
..	9	12	2.9	15.0	22.1	5.1
4	10	12	1.3	14.8	25.0	8.9
..	11	8	3.4	14.2	24.5	6.9
5	12	3	5.6	13.0	17.6	−1.0
..	13	3	5.9	10.8	23.3	6.6

DISCUSSION.

I. NITROGEN ABSORPTION.

Table I represents the analyses of two, three and four-day pooled faecal specimens, compounded into twelve and fourteen-day periods and the results expressed as an average per 24-hour period.

The average of such long periods was considered necessary in order to obtain a representative value for a 24-hour stool, the use of markers'' over shorter periods being unsatisfactory especially with soft or liquid stools.

The legitimate assumption was made that any assay of faecal nitrogen can be interpreted as an assay of protein.

Taking the upper limit of normal faecal nitrogen as 1.5 G. per 24 hours, it will be seen that of the twenty studies made, some fourteen are above this level, ranging in value from 1.6. G. to 4.O G. per twenty-four hours (average 2.4 G.).

Assuming a normal protein intake (about 16 gr. N_2) these faecal nitrogen figures do not represent a significant loss. However, in the untreated phase of this disease with anorexia and diarrhoea, the protein intake may fall to such a level that the net nitrogen absorption may well fall below the critical value of 6. Gr. per diem, thus producing a negative balance. This will be enlarged upon in the next section. Except for examples 19 and 20, there appears to be no significant relationship between faecal nitrogen and nitrogen intake.

The general rise in faecal nitrogen could be attributed to any of the following causes :—

(a) Primary failure to absorb ingested nitrogen.
(b) Increase of intestinal bacteria growing on the dietary substrate.
(c) Intestinal irritation giving rise to increased nitrogenous secretions and casting of epithelial cells.

The first cause can be excluded as it will be observed that nitrogen excreted is roughly related to the weight of stool,—the greater that weight the larger the nitrogen output, and vice versa. Further the actual percentage nitrogen per 100 Gr. stool only varies between.7 and 1.5%. If failure of absorption had occurred and persisted, the stools of smaller weight would be expected to contain a considerably higher percentage of nitrogen than that actually found.

The data available does not offer an explanation as to which of the causes is operative. However, the clinical observation that diarrhoea in sprue is amenable to sulphaguanidine therapy suggests and increased bacterial action.

This, from a metabolic standpoint, is of no significance because whichever of these processes is operative the net result still represents a nitrogen loss.

II. UTILISATION

Table II gives results of nitrogen balance experiments on five cases. These results have been compounded and arranged in a similar manner to those in Table I.

With the exception of experiments 8 and 12 to be discussed later, the salient feature is the retention of nitrogen by all cases. This indicates that at some period prior to admission to hospital a negative balance existed. These cases all had a previous history of several months' diarrhoea and anorexia. It is therefore reasonable to assume that this state of negative balance resulted from an elevated faecal nitrogen and lowered protein intake. Experiment 12 demonstrates this point ; the balance experiment was made on a patient undergoing a relapse accompanied by diarrhoea and anorexia.

Experiment 8 was a study on a case rapidly recovering, i.e. in marked remission, with elevated faecal nitrogen, a negative balance and high urinary nitrogen. The patient was eating the full diet of carbohydrated and fat. The high urinary nitrogen and negative balance may indicate in this period relatively poor utilisation of fat and carbohydrate with an increased metabolism of protein.

The general results of these experiments indicate a good absorption, retention, and turnover of nitrogen. This is especially apparent in Cases 3 and 4 who had a higher average protein intake. This would suggest that from the dietary standpoint as high a protein intake as possible is desirable in sprue cases.

SUMMARY

1. 20 experiments on faecal nitrogen in sprue showed an elevation in 70% of the experiments.

2. This elevation is considered only to be significant in conjunction with a low protein intake.

3. The increased nitrogen level is probably the result of increased bacterial action.

4. Nitrogen balance experiments on five cases showed good retention and turnover, indicating the existence of a previous negative balance.

5. The satisfactory absorption of nitrogen is support for a high protein diet in these cases.

SALT DEFICIENCY IN SPRUE

SECTION II

Hypotension defined as a blood pressure below 100/70 mm. Hg. has occurred in 66 out of the total of 680 cases reviewed in this report. These cases of sprue have all been of relatively short duration—less than a year The hypotension has occurred in the majority of instances in those who are in the relapse phase of the disease with prolonged diarrhoea, vomiting and anorexia. These have all shown clinical evidence of dehydration and peripheral circulatory failure. In acute sprue, as seen in India during the Second World War, this is the group from which the occasional fatal case is drawn.

It is particularly relevant therefore to find some adequate explanation for the development of this syndrome.

Since these symptoms have so much in common with those of salt deficiency syndromes experimentally produced (McCance) an investigation into this condition was undertaken.

METHODS. The following analytical methods were used :—

Serum sodium	Uranyl zinc acetate preciptiation.
Serum pottassium.	Cobaltinitrite precipitation.
Serum chloride	Volhard-Harvey titration.
Blood urea	Urease-Nesslerisation.
Plasma volume	Vital red method.

Chloride was determined in urine and stools by the open Carius method ; sodium and potassium were determined on ash extracts of stools and urine.

TABLE I

BLOOD VOLUME AND ELECTROLYTES.

Patient.	Serum mg/100 ml.	Sodium mEq/L.	Serum mg/100 ml. (as NaCL)	Chloride mEq/L	Serum mg/100 ml.	Potassium mEq/L.	Blood Ura mg/100ml	Plasma litres	volume ml/kg.	Haemato-crit er cent	Blood pres-sure mm. Hg.
1	300	130	580	99	—	—	60	2.5	61	37	90/52
2	300	130	545	93	16	4.1	42	3.0	52	36	74/45
3	320	139	608	104	—	—	45	2.2	41	40	88/56
4	310	135	571	98	15	3.8	40	2.2	40	44	92/68
5	315	137	573	98	18	4.6	30	1.9	42	50	96/54
6	304	132	664	96	—	—	50	1.7	34	46	100/60
7	278	121	517	88	20	5.1	45	2.0	44	40	94/54
8	314	136	573	98	22	5.6_2	54	2.5	46	43	94/60
9	312	135	566	97	20	5.1	29	2.4	46	46	110/68
10	258	112	515	88	20	5.1	36	2.1	53	42	100/70

GENERAL CLINICAL FEATURES.

The ten patients investigated were all suffering from tropical sprue contracted during their period of service in the India-Burma theatre. All had steatorrhoea, fat accounting for more than 30% of the dry stool weight. All had lost 10 kgm. or more of body-weight.

Sevrely had periods of remission during their illness which in all was less than a year. Evidence of glossitis was common but inconstant. Anaemia was not marked. Anorexia and diarrhoea were marked symptoms. Abdominal distension was variable.

These cases were selected for investigation by low blood pressure in conjunction with the other symptoms and signs described above as forming the picture of acute severe sprue. Clinical evidence of dehydration and peripheral circulatory failure such as flaccid, wrinkled skin, pallor, collapsed superficial veins etc. was present.

LABORATORY FINDINGS.

In Table I are given the results of the estimation of plasma volume and haematocrit, and of serum sodium, chloride and potassium in ten patients. In the calculation of the plasma volume per kilogram the patients actual weight at the time of estimation has been used ; had the normal body-weight been used, the values would have been lower by 10 per cent or more.

Seven ofthe patients had a plasma volume of less than 2.5 litres, and two of them less than 2.0 litres. Five of the patients had a plasma volume of less than 45 ml./kg. The haematocrit readings lay mostly between 40 and 46 per cent ; but one high value of 50 per cent, and two low values of 36 and 37 per cent, were observed. Later estimations of the haematocrit percentage showed that these normal values did in fact represent a moderate haemoconcentration, for when the plasma volume rose with therapy the haematocrit percentage fell to values just below the usual normal limits.

TABLE II

BLOOD ANALYSIS IN PATIENT 10.

Date	Serum Sodium mg/100ml.	Serum Sodium mEq/L.	Serum Chloride mg/100ml. (as Na CL)	Serum Chloride mEq/L.	Blood Ura mg/100ml.	Plasma Volume litres.	Haematocrit per cent.
22nd Sep.	258	112	—	—	36	2.1	42
23rd Sep.	296	129	515	88	32	—	—
27th Sep.	320	139	620	106	40	—	—
29th Sep.	310	135	612	104	45	—	—
1st Oct.	—	—	—	—	—	2.5	34
1st Nov.	337	146	615	105	24	2.7	41

The serum potassium on 23rd Sep. was 20.2 mg./100 ml. The alkali reserve on 29th Sep. was 47.3 vol./100 ml.

The serum sodium values were uniformly low, ranging from 258 to 320 mg./100 ml. (112 to 139 mEq./l). A control series of five sprue patients with gross steatorrhoea, but with a normal blood pressure, gave values for the serum sodium ranging from 318 to 354 mg./100 ml. Moreover, normal values were found for the serum sodium in four of the patients reported in Table I, on whom it was possible to obtain a blood sample after recovery. The serum chlorides were also low, but less markedly so than the serum sodiums (range 515-608 mg./100 ml. 88-104 mEq./l.) The serum potassium was done in seven patients, and in none of them did it exceed the upper limit of normal. The highest blood urea was 60 mg./100 ml., and in five other patients the blood urea was over 40 mg./100 ml.

This group of observations indicated that in these patients hypotension and circulatory failure were associated with a low serum sodium and chloride, and less constantly with a low plasma volume. They gave no evidence as to whether the observed sodium deficiency was caused by inadequate intake or loss of electrolytes, or whether diminished activity of the suprarenal gland might be responsible for the hypotension, as was suggested by Thaysen (1932). It was found in the later patients of the series that treatment with salt, either by mouth or intravenously, was followed by the disappearance of the circulatory collapse, and the serum sodium rather slowly returned to normal levels. It was also found that the excretion of chloride in the urine was low, of the order of 3-5 gm. per day, but that chlorides were never absent from the urine. The urine and faeces of patient 10 were collected over a 15-day period after his admission and again for a 3-day period after he had completely recovered from dehydration, but while he was still passing large amounts of fat in the faeces. Tables II to V give the results of blood, urine, and stool analysis, and the mineral intake and output for corresponding periods.

TABLE III

URINE ANALYSIS INPATIENT 10.

Period	Volume	S. G.	Sodium.		Chloride		Potassium		Urea	Urea clearance % of average normal.
			g.	mEq.	g.	mEq.	g.	mEq.		
I	3138	1012	0.14	6.1	4.7	132	0.12	3.1	57	80
II	4415	1012	0.31	13.5	14.6	412	1.06	27.2	59	63
III	3000	1010	0.21	9.1	10.2	288	0.68	17.4	40	46
IV	4830	1006	1.03	44.8	8.6	242	0.65	16.7	44	50
V	8640	1007	1.08	47.0	9.2	259	0.75	19.2	97	85
After.	7570	1031	17.5	762.0	30.5	860	3.0	77	53	86

All periods are of three days, and the figures for Sodium, Chloride, Potassium and Urea represent the total excretions in each period. Periods 1 to 5 are consecutive starting from 22nd. Sept. the after period was the three days 12th. to 14th. Nov. at which time the patient had a normal blood pressure, but was still passing fatty stools.

The blood estimations (Table II) showed a low serum sodium which rose rapidly when salt was added to the diet. The serum chloride was not so low as the serum sodium initially, and it rose to within normal limits more rapidly. The initial plasma volume was lower than the value obtained after recovery, but the difference was not a striking one. The haematocrit percentage fell when dehydration was corrected, and later rose again to a normal value as the patient's general state improved. The blood urea during the dehydration period lay within the normal range, but was higher than after recovery. Kirsner et al. (1943) comment on the fact that blood urea may show little increase in moderate degrees of salt deficiency. However, the urea clearance (Table III) was depressed at the time when the blood urea was highest, and the 3-day output of urea also fell. Comparison of the results in Table II with the clinical data in the appended case-report on the anomalous blood findings was attended by only partial clinical improvement. The pulse rate fell, the blood pressure rose, and the peripheral circulation improved. There was some gain in weight, but the patient continued to pass very large fluid stools, his appetite was poor, and the felt no better. It was obvious that salt deficiency had been responsible for only a part of the complex clinical picture, and rapid improvement in his general conditions occurred only after he was treated with sulphaguanidine and parenteral liver.

MINERAL BALANCE AND EXCRETION. (Table III-IV)

There was retention of sodium, chloride and potassium throughout the first observation period of 15 days. In the case of sodium and chloride, this occurred on dietary intakes varying from less than 10 g. to more than 20 g. of sodium chloride per day, even though quite abnormal amounts of sodium and chloride were being lost in the stools.

TABLE IV

FAECAL ANALYSIS IN PATIENT 10.

Period.	Wet weight g.	Dry weight. g.	Total fat g.	Sodium g.	Sodium mEq.	Chloride g.	Chloride mEq.	Potassium. g.	Potassium. mEq.
I	3520	239	87	4.6	200	1.2	34	1.0	25
II	9155	277	118	8.9	387	8.1	228	1.8	46
IV	3550	136	71	3.4	148	2.1	59	2.0	51
V	910	113	49	0.8	35	0.4	11	2.8	72
After.	1225	265	96	0.5	29	0.03	1	4.1	105

The retention of sodium and chloride was accompanied by a rise in their serum concentrations. In the after-period of three days, the patient was in 'sodium balance', and was excreting rather more chloride than he took in ; there was still a retention of potassium, which may have been related to the fact that he was still putting on weight rapidly. Although the dietary intake of sodium and chloride, when expressed in milli-equivalents, was approximately equal, more sodium than chloride was retained, except during period 1, when the patient was on a diet containing less than 10 g. of salt per day. This suggests that in the period before our observations, when salt deficiency was actually developing, loss of sodium had exceeded loss of chloride. Even in the observation period loss of sodium in the stools was much greater than loss of chloride ; and normal intestinal secretion is known to contain more sodium than chloride (Gamble et al., 1945). The total loss of sodium and chloride in the stools was greatly in excess of the negligible amounts found in normal stools. Even in the after-periods, although chloride was practically absent from the stools, they still contained 0.5 g. of sodium in three days ; at this stage, the stool was still bulky and contained much fat, but the ratio of dry to wet weight was within normal limits. The greater loss of sodium than of chloride in the stools was clearly reflected in the urinary excretion of these ions. In the first observation period, the urine contained only 6.1 mEq. of sodium in three days, whereas in the same time 132 mEq. of chloride was excreted. After some days on diet with added salt, the chloride output in the urine was still more than five times as

TABLE V

INTAKE AND OUTPUT OF ELECTOLYTES IN PATIENT *0.

Period	Intake Sodium		Intake chloride		Intake Potassium		Output Sodium		Output Chloride.		Output Potassium	
	g.	mEq.	g.	mEq.	g.	mEq.	g.	mEq.	g.	mEq.	g.	mEq.
1	10.1	440	16.7	470	10.3	264	4.6	206	5.9	166	1.1	29
2	27.8	1210	43.0	1210	9.9	254	9.2	401	22.7	640	2.9	73
3	20.0	870	31.2	852	7.9	206	9.2	401	14.2	401	5.6	143
4	12.8	557	20.0	563	4.2	108	4.4	193	10.7	301	2.7	68
5	10.9	474	17.9	504	8.8	226	1.9	82	9.6	270	3.6	91
After	18.2	792	28.4	800	11.0	282	18.0	791	30.5	861	7.1	182

The Potassium intake was derived entirely from the food, and its variability was due to the patient having been unable to take different items of measured diet at different times. The sodium and chloride were derived partly from the diet, and partly from supplements of Sodium Chloride, to the amount of 5 g./day in period 1, 25 g./day in period 2, 15 g./day in period 3, and 10g./day in periods 4 and 5 and the after period.

great as the sodium output. Only in the after-period were sodium and chloride excreted in equivalent amounts. These findings indicate that salt deficiency in this patient was complicated by acidosis ; the kidneys conserved base rigidly, but continued to excrete chloride in significant amounts. Further evidence of acidosis may be found in the alkali reserve of 47.3 vol./100 ml., and in the finding of 113 mEq. of (ammonia plus titratable acidity) in one 24-hour specimen of urine.

DISCUSSION.

The clinical and laboratory findings in these patients are those of dehydration due to salt deficiency. Similar episodes of dehydration are not uncommon in coeliac disease, and Prunty and Macoun (1943) describe a case of non-tropical steatorrhoea with hypotension and low serum sodium and chloride. The comparative frequency of salt deficiency as a complication of tropical sprue does not seem to have been appreciated, for electrolyte studies in this disease have been almost confined to calcium and phosphorus metabolism.

The chief cause of salt deficiency in these patients is almost certainly the loss of sodium and chloride in the bulky, often fluid stools. It may be left an open question whether the sodium and chloride in the stools represent unabsorbed dietary salt or intestinal secretion which has not been reabsorbed in the usual way. The greater loss of sodium than of chloride suggests that intestinal secretions form a large part of the fluid stool. On the other hand, increasing the intake of saline fluid in patient 10 was followed by a three-fold increase in the bulk of the stool, which decreased again when the saline intake was reduced. Visscher et al. (1944) have shown that absorption of sodium, chloride, and even water is not a simple process of diffusion, but may differ by 200-fold from rates calculated from concentrations of these substances ; and it is not impossible that an active process of this kind should be impaired in severe sprue, or even in chronic starvation. Although diarrhoea is the main cause of salt deficiency in these patients, the salt intake is also concerned. Anorexia interferes with the intake of salt and salt-containing foods, and thirst is relieved by fluids which contain little or no salt. Our observations suggest that adrenal insufficiency, suggested by Thaysen (1932) was a cause of hypotension in steatorrhoea, was not an important factor in our patients. No increase in the serum potassium was observed ; and in patient 10, sodium was adequately retained by the kidneys. Moreover, Prunty and Macoun (1943) in their case of salt deficiency in idiopathic steatorrhoea found no biochemical evidence of adrenocortical deficiency. Sprue patients with hypotension do not respond clinically to therapy with desoxycorticosterone acetate (Leishman, 1945).

THERAPEUTIC IMPLICATIONS.

When the likelihood of salt deficiency occurring in cases of sprue with profuse diarrhoea is appreciated, much can be done in the way of prophylaxis. The diets normally used in the treatment of sprue are of no more than average salt content, and they require to be supplemented by the liberal addition of salt in cooking and seasoning, in any patient who develops diarrhoea, When anorexia interferes with the intake of food, it becomes even more important to give salt as well as fluid. Skimmed milk, which forms a high proportion of the early sprue diet, contains less than 0.2 g. of salt per 100 ml ; the addition of 0.3 g./100 ml. (11 g. per pint) is well tolerated. Orange or lemon juice fortified by 0.45 g. of salt per 100 ml. is suitable drink, and we have found that sprue patients take it well. A daily intake of 15 g. of salt should be aimed at in the sprue patient with diarrhoea in the tropics. The actual food in a sprue diet supplies only 5 g. of this, and the remaining 10 g. has to be added in seasoning, and in weak saline drinks.

In established salt deficiency, more intensive salt therapy by mouth has to be given. Although these patients do not usually complain of thirst, they

take saline fluids well. The limit to the amount of saline fluid which can be given by mouth is set by increase of diarrhoea, and improvement on oral therapy may take some days. In only one patient of this series was it found necessary to give saline by vein. Even more important than replacement therapy is the necessity of cutting short the watery diarrhoea which is present in nearly all these patients. Although the stools have not shown the exudate of bacillary dysentery, sulphaguanidine has been found effective in four patients of this series whose diarrhoea did not respond to diet and rest in bed. Parenteral liver should also be given as part of the general treatment.

With treatment on the lines suggested all the patients in this series made a good recovery from their acute state of circulatory insufficiency. The stool fats, as might be expected, were not restored to normal, although they become lower when diarrhoea was arrested. The patients were, however, brought from a state in which they seemed likely to succumb to one in which routine therapy for sprue could be applied and take effect.

SUMMARY.

Between 5 and 10 per cent of patients with sprue acquired on military service have had a low blood pressure, asthenia, and signs of peripheral circulatory failure. Ten such patients were found on investigation to have a low serum sodium and serum chloride, and in some cases a plasma volume which was low in relation to their actual body-weight. Of these abnormalities the low serum sodium was the most pronounced. A balance experiment on a typical patient showed abnormal loss of sodium, and to a less extent of chloride, in the faeces ; in the urine, sodium was rigidly conserved, while chloride was excreted, though in amounts less than normal. When the patient was put on ahigh intake of salt, sodium and chloride were both retained, and the serum sodium and chloride rose to normal levels ; the blood pressure rose, and clinical signs of dehydration disappeared, although the abnormal loss of fat in the stools was not affected.

It is considered that such patients show the clinical and biochemical pattern of salt deficiency, modified by some degree of acidosis, owing to the preponderant loss of sodium over chloride in the stools. Loss of electrolyte in copious watery stools is thought to be the main cause of the salt deficiency, but diminished intake of salt in anorexic patients is also a factor. The results reported do not suggest adrenal insufficiency, for the serum potassium was not increased, and conservation of base by the kidneys was adequate. Treatment by increasing the salt intake to 15 g. per day corrects the dehydration in a few days, and intravenous saline had to be given in one patient only. If watery diarrhoea does not respond to diet and rest in bed, replacement salt therapy should be supplemented by sulphaguanidine, which has been found to check this type of diarrhoea.

CASE REPORT (Patient 10)

Age 22 years. Tropical service 1 year.

Previous history. Since 1939, 'dyspepsia' epigastric pain, heartburn, and occasional vomiting after fatty meals. A barium meal had been done and was normal. There was no previous history of diarrhoea, dysentery or malaria.

His present illness began in May, 1945, when he was in Eastern Bengal. The onset was sudden, with the passage of copious forthy watery stools. Loss of appetite and abdominal distension were present from the beginning, and he became very weak. Flatulence and abdominal discomfort were prominent symptoms from the onset, whereas tongue signs did not appear until 3 months after the diarrhoea began. He was evacuated to base, and admitted to this hospital on 20 Sept. '45.

Condition on admission. The patient was severely ill, and showed clinical signs of dehydration dry wrinkled skin, coated tongue, and diminished intrao-

cular tension. The pulse was weak and dicrotic, and the superficial veins were noticeably collapsed. Blood pressure was 100/70, and fell to 90/65 when the man sat up ; the pulse rate was 90 rising to 96 on sitting. The man's appetite was poor, but he took fluids well. The tongue was painful and reddened at the tip and sides, depapillated but not fissured. Abdominal distension was present, with flatulence ; the patient was passing ten pale fluid copious stools daily.

The patient's weight was 87 lb., his normal weight being 154 lb. A blood count showed Hb. 12 g./100 ml., R.B.C. 3.0 million/cu. mm. A 3 day specimen of faeces weighed 3.5 kg., the dry weight being 239 g. This contained 36 per cent fat, the total output of fat in 3 days being 87 g., of which 82 g. were 'split', No mucus or inflammatory exudate was found in the stools.

Progress under treatment. The patient was put on a sprue diet containing 118 g. protein, 45 g. fat, and 159 g. carbohydrate per day, the total calorie intake being 1513 per day This diet contains less than 5 g. of salt per day, and it was supplemented during the first three days of observation by 5 g. of salt to bring the salt content nearer a normal level. Even on this diet, comparatively restricted in salt, the serum sodium rose, and concurrently the patient's circulatory state improved, so that by 24 Sept., four days after admission, his pulse rate had fallen to 72 per minute, and his blood pressure was 104/70 lying, but rose to 110/75 on sitting up. After three days on a 'normal salt' diet, the patient was put on a 'high' diet, with 25 g. of added salt per day. This had to be reduced after three days to 15 g., for the patient's appetite became capricious, and he passed increased amounts of watery stools. Specific sprue therapy with parenteral liver extract was begun, and sulphaguanidine was given in a total dosage of 70 g. in four days ; the stools became formed within three days, the wet weight being 300 g./day. The general condition improved rapidly, and a month after the start of treatment the patient's weigh had risen from 87 to 128 lb. His blood pressure was normal, tongue signs had disappeared, and he felt well, although his stools remained bulky and he was passing 96 g. of fat in three days.

DISCUSSION ON ABSORPTION.

Not only is sprue a disease 'of unknown aetiology', but even the mechanism or functional pathology of the steatorrhoea has been the subject of conjecture rather than of experiment. In this investigation we have made it our main object to gather as reliable information as possible about the natural history of the fat absorption defect in early sprue, for the only test of therories lies not in their logical consistency but in their correspondence with observed facts. It is a matter of general agreement that the failure to assimilate fats in sprue is not caused by faulty 'digestion' of the fat, for the lipolytic activity of duodenal contents is normal in sprue (Sokhey and Malandkar, 1928). It is fairly certain, too, that the steatorrhoea in sprue does not represent an excessive secretion of fat by the intestine, for on a fat-free diet the steatorrhoea disappears (Wintrobe, 1942). For these reasons, it has come to be accepted that the functional lesion in sprue lies in the transfer of fat or of fatty acids from the lumen of the bowel to the blood or lymph vessels ; but widely different views have been expressed as to the mechanism of this failure in absorption.

'MECHANICAL' THEORIES OF SPRUE

Bennett and Hardwick (1940) have suggested that sprue forms one example of 'chronic jejuno-ileal insufficiency', and compare it with surgical removal of part of the small intenstine. Hurst (1942) postulated a loss of the pumping action of the villi. Stannus (1942) criticises these mechanical theories of the absorption defect in sprue at some length, and we are in agreement with his criticism. In addition to the evidence which he brings forward against such

explanations, we would point out that a non-specific 'insufficiency' of the small intestine would affect substances other than fat ; yet we have observed that in the early stages of sprue there is gross steatorrhoea, but no evidence of impaired absorption of iron, amino-acids, nitrogen or chloride ; while the absorption of idoide, although it may be gastric rather than intestinal, is also normal. Moreover, our findings that percentage fat absorption remains the same when the fat content of the diet is moderately increased tells against the mechanical theories ; for if there were a rigid mechanical defect in absorption, one would expect that the added fat in the higher diet would be excreted quantitatively, thus lowering the percentage fat absorption. For these reasons, in addition to those brought forward by Stannus, it seems to us that the failure of fat absorption is not a 'mechanical', but rather a 'biochemical' one.

NORMAL FAT ABSORPTION.

The difficulty of explaining the fat absorption defect in sprue is very much increased by the fact that the normal mechanism of fat absorption is still a matter of controversy. The general view is that all fats are split before absorption, the glycerol is then absorbed in watery solution, while the fatty acids are absorbed as fatty-acid-bile-salt complexes, as cholesterol esters, or as phospholipides. Frazer (1940) has suggested that a certain amount of fat may be absorbed without previous splitting, as a fine emulsion, and that this type of absorption is associated with an increase in the chylomicrons, the small fatty particles seen in the blood on dark-ground illumination ; this absorbed neutral fat gains access to the blood-stream by way of the intestinal lymphatics and thoracic duct. In addition to neutral fat, there is also absorption of split fat, and this is by way of the intestinal blood vessels into the portal circulation, so that absorbed split fat has to pass through the liver before reaching the systemic circulation. Frazer brings forward a considerable body of experimental evidence to show that absorption of neutral fat is a possibility ; but the proportion of fat absorbed as 'neutral' and as 'split' fat has not been determined. If one accepts Frazer's identification of chylomicrons with absorbed neutral fat, an approximate calculation of the amount of fat absorbed in this way can be made ; for figures given by Elkes, Frazer & Stewart (1939) suggest that an increase in chylomicrons of 100 per field corresponds in a general way to a fatty acid increase of 20 mg./100 ml. This relationship can only be an approximate one, in view of the errors inherent in counting chylomicrons, and the large variation in the size of the particles. It is, however, in agreement with the amount of milk fat which must be added to clear serum to produce an opacity similar to that after our fatty meal ; and the average increase in neutral fat fatty acid in our eleven normal subjects was 40 mg./100 ml. the average chylomicron rise being about 150.

The total amount of fat present in the chylomicrons found in the plasma after a 20 g. fat meal can be put at somewhere between 0.5 g., not a high proportion of the total fat known is to be absorbed, which is 90% or more of the amount given, in normal people. Moreover, in a number of sprue patients under liver treatment, flat chylomicron curves became normal, yet there was no corresponding measurable change in percentage fat absorption ; which implies that the amount of dietary fat involved in producing a normal chylomicron count was not large enough to be detected by fat balance work. On the other hand, the fat attributable to chylomicrons does represent a high proportion of the total blood fat increment. These conflicting observations can only be reconciled if one assumes that particulate fat is more slowly removed from the blood-stream than fat absorbed in other ways ; so that the relatively small amount of fat absorbed in chylomicron form persists longer in the blood-stream, while the end-products of split-fat absorption are rapidly transferred to the liver or depots. The presence of lipase in the bowel implies that soon after a fat meal both neutral and split fat will be available for absorption, and since Frazer has demonstrated the possibility of netural fat absorption, it seems likely that both processes will

go on; but as Bloor (1943, p.91) points out, it is probable that most of the fat is absorbed in the split form, and the amount of fat involved in chylomicron-formation is not large enough to challenge this general conclusion.

QUANTITATIVE ASPECTS OF FAT ABSORPTION IN SPRUE.

Our absorption studies in early sprue show that the defect in fat absorption is a partial one, since two-thirds of the ingested fat does not appear in the faeces. Stannus (1942) has suggested that the fat absorption defect in sprue can be explained on the assumption that neutral fat is well absorbed, while the power to absorb split fat is lost, probably owing to defective phosphorylation. His hypothesis is an attractive one at first sight, for the partial nature of the defect in fat absorption, and the fact that nearly all the stool fat is split, appear to support it. When considered quantitatively, however, it cannot form the whole explanation ; for the considerations given in the previous paragraph make it certain that neutral fat absorption cannot account for two-thirds of the total fat absorption. Also, no conclusion can be drawn from the stool fat as to which form of fat has escaped absorption, for splitting of fat goes on actively in the stool in vitro, so that even the fresh stool is unlikely to give a true picture of the split fat and neutral fat ratio in the small intestine ; and this is especially so in sprue, where the high soap content of the stool increases the rate of splitting, probably by promiting emulsification.

Our results do in general support one part of Stannus's hypothesis, that neutral fat is well absorbed. The chylomicron count is often normal in early sprue without diarrhoea, and the neutral fat increment in the fat curves in sprue is more nearly normal than either total fatty acid or phospholipide increment. More severe cases of sprue show a low chylomicron count, and in these the percentage fat absorption may be no lower than in those with normal chylomicorn counts, nor does their percentage fat absorption improve appreciably when the chylomicron count returns to normal with liver treatment. This group of observations strongly suggests that although neutral fat absorption, as judged by the chylomicron count, is normal in early sprue, it cannot account for any high proportion of the two-thirds of the total fat which is known to be absorbed in such cases. It follows from this that the failure in split-fat absorption is far from complete, at any rate in early sprue. It may be pointed out in this connection that even a complete failure in phosphorylation would not lead to cessation of a absorption of split fat, for some fatty acid is absorbed in the form of complexes with bile salts, and some in the form of cholesteryl esters. There is no evidence of any deficiency of bile output in sprue, for though the stools are pale, they contain normal amounts of bile pigment in the colourless reduced form. There is no certain evidence as to how much part cholesteryl esters normally play in fatty acid absorption, although it is known that in some cases a fatty meal is followed by an increase in cholesteryl esters in the serum (Knudsen 1917). The low values for cholesterol in the serum in sprue, and the fall which occurs in serum cholesterol after a fatty meal in that disease, suggest in sprue less fatty acid may be absorbed in this way than in normal people. We believe the time has not yet come for a final evaluation of the relative importance of the absorption defects in the different fatty fractions in sprue ; for it is still not known for normal subjects what proportions of ingested neutral fat are absorbed as neutral fat, as phospholipide, as cholesteryl ester and as bile-salt-fatty-acid complexes.

PHOSPHORYLATION.

The work of Sinclair and later of Verzar has established the importance of phosphorylation as an intermediate stage in the absorption of fatty acid ; though here again, all that is certain is that the process occurs, and it is not known what proportion of fatty acid is absorbed with phospholipide as an inter-

mediate stage. The evidence for phosphorylation is mainly based on analyses of the fats in intestinal mucosa, and on absorption studies with isolated intestinal loops ; neither method can be applied to the patient with sprue. It is hardly possible to obtain direct evidence of a failure of phosphorylation in that disease, such as is postulated by Stannus (1942). Our own results give no direct evidence of phosphorylation defect, but sprue patients showed a distinctly smaller increase in serum phospholipide after the fat meal than did normal patients. Although serum phosphlipide is not directly derived from the intestine (Reinhardt et al 1944) the increase in serum phospholipide after a meal may well bear some relation to the amount of fatty acid absorbed directly into the portal system, carried to the liver, and there phosphorylated. In the third part of this report, evidence is given to show that yeast extract in large doses exerts a favourable effect on fat absorption in sprue ; and it is known that yeast extract corrects the phosphorylation defect found in adrenalectomised rats poisoned by phosphorus (Bloor, 1943, p.94).

ABSORPTION OF NON-FATTY SUBSTANCES.

It has already been shown that absorption of neutral fat, as judged by the chylomicron count, may be normal in early cases of sprue, even with considerable steatorrhoea ; and that shows an impairment in other cases, particularly in those with diarrhoea, but also in some patients with formed stools. It seemed possible that an absorption defect, originally limited to fatty acid and possibly glucose, might later become generalised. To test this possibility, the absorption of several nonfatty substances has been examined. It was found that iron, nitrogen, amino-acids, chloride and iodide were well absorbed at a time when fat absorption, as judged by fat balance, was imparied. In cases of sprue in clinical relapse, however, it was found that iron and nitrogen absorption might be defective ; in one patient the serum iron curve returned to normal levels with liver treatment. In patients with diarrhoea, secondary absorption defects are to be expected, and it wss found that quite large amounts of sodium and chloride might be lost in the faeces : adding salt to the diet increased the faecal sodium and chloride. Glucose occupies rather a special position, owing to the possibility of phosphorylation playing a part in its absorption. It was found that glucose tolerance curves might be normal in the presence of definite steatorrhoea ; but flat curves also were found in patients with only minor degrees of steatorrhoea, and with no other evidence of secondary absorption defects. It is doubtful how efficient blood sugar curves are in detecting minor degrees of a malabsorption of glucose, whereas the fat balance technique is capable of detecting quite small changes in fat absorption ; so it is quite possible that glucose absorption is specifically impaired in sprue, although our methods of detecting it are not sensitive enough to demonstrate its presence in every patient with steatorrhoea.

Apart from data on the absorption of specific substances, some information on general absorption in sprue as opposed to fat absorption, may be gained from the amount of non-fat dry residue in the stools. This method has the limitation that a large part of the dry stool residue is bacterial, but it is capable of showing gross changes in general absorption. The figures already given show that in many patients there is a decrease in the non-fat dry residue with improvement in fat absorption, and this may be due partly to an improvement in general absorption. In other patients, who show no change or even an increase in the non-fat dry residue, there may never have been any serious interference with general absorption.

DIARRHŒA IN RELATION TO ABSORPTION.

Many patients with sprue have attacks of diarrhoea in which bulky formed stools are replaced by copious fluid motions. Such patients are very likely to become salt-deficient, and they excrete a larger proportion of ingested fat

during the diarrhoeic phase than either before or after it. Other absorption tests, such as the chylomicron count and the blood-sugar curve, also give evidence of impaired absorption in diarrhoea, over and above what is observed in the same patient when his stools are formed. Clinically, these diarrhoeic attacks can be regarded either as complications or as integral parts of the sprue syndrome. Biochemically, they represent a phase in which the general absorption defect is especially pronounced. In a tropical country, such episodes of diarrhoea are sometimes found to be associated with the presence of dysentery bacilli and exudate in the stools. In other patients, although the stools contain no exudate, sulphaguanidine in full doses is followed by the passage of formed stools. In the belief that these diarrhoeic attacks may in some cases represent the results of intercurrent infection, or of lowered intestinal resistance to potential pathogens in the normal flora, we have excluded findings obtained during diarrhoea from this discussion of absorption in sprue.

SUMMARY OF DISCUSSION ON ABSORPTION.

The steatorrhoea which is the salient feature of sprue is not caused by faulty digestion of fat, or by intestinal secretion of fat in abnormal amounts. There are four modes of fat absorption known to occur in normal people—absorption of unsplit fat, and absorption of fatty acids as phospholipide, as cholesterol esters and as complexes with bile salts. The relative importance of these mechanisms in normal people is not certain. In early mild cases of sprue, neutral fat absorption is not demonstrably impaired and there is no deficiency of bile salts. There is some evidence that absorption of fatty acid as phospholipide and as cholesterol esters is imparied. The absorption defect in early cases involves about one-third of the fat in the diet, and there may also be some impairment of glucose absorption, as judged by flat blood sugar curves after a glucose meal. Defective phosphorylation of fatty acid and of glucose is a likely mechanism of their defective absorption, but final proof of this is lacking.

In more severe cases of sprue, secondary absorption defects are added, of substances such as neutral fat, iron, and nitrogen. These secondary absorption defects may occur in patients with formed stools. In patients with diarrhoea, secondary absorption defects are always present, and there is also a further diminution in the absorption of fatty acid and glucose. Patients with diarrhoea become dehydrated, and this may be the cause if death in patients with early sprue.

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PART III.

CLINICAL RESULTS

I. CLINICAL RESULTS.

SECTION I.

The treatment of sprue has long been based on the control of diet and the administration of liver (Manson-Bahr, 1943). Many different types of diet have been tried and success has been claimed for all, but since liver therapy was shown to be an effective method of treatment by Castle and Rhoads (1935) servere dietary restriction has been found unnecessary in most cases and diets have been planned on the principle of a high protein and low fat content (Fairley 1934). In this section of the report an attempt is made to assess the value of treatment based on such a diet, with and without the addition of drugs containing vitamins of the B group. The effect of therapy was carefully followed in 62 of the 80 patients of series B. As was shown in Part I of this report, many of the patients in this series did not conform to the classical picture of tropical sprue, in that they were not severely ill, with only slight steatorrhea and little anaemia. The following means of treatment were studied :

(1) Diet.
(2) Parenteral liver preparations.
(3) Nicotinic acid, riboflavine.
(4) Yeast extract.

CRITERIA OF PROGRESS.

During treatment, a marked clinical improvement in these patients did not always coincide with a demonstrable improvement in intestinal absorption, as measured by fat balance experiments. Therefore in assessing treatment it is necessary to consider separately any general improvement in the patient's condition and any change in intestinal absorption. The effect of various drugs on fat absorption are reported separately at the end of this section and the result will be mentioned here only in so far as they are relevant to the ques-question of therapy. Satisfactory clinical progress was marked by weight gain and return of appetite. In those patients who had watery diarrhoea, such improvement only took place with the cessation of diarrhoea.

TABLE I

VALUES OF THE DIETS USED IN THE TREATMENT AND INVESTIGATION OF SPRUE

Diet	Calories	Carbohydrate in G.	Protein in G.	Fat in G.	Vit. A in I. U.	Thiamine in mg.	Riboflavin in mg.	Nicotinic acid. in mg	Ascorbic acid acia in mg.	
3	1513	159	118	45	14,700	1.0	5.1	19.1	31	Diet used in the routine treatment of Sprue.
4	2109	233	139	69	16,200	1.3	6.2	27.2	31	
5	2692	308	149	96	17,800	1.5	6.3	27.2	43	
n. 1	2037	215	139	69	1,600	1.1	3.1	10.1*	28	Investigation diets for therapeutic trials.
In. 2	2620	290	149	96	3,200	1.3	3.2	11.1	40	

*In some cases meat in the diet was replaced by fish : the content of Nicotinic acid was then 4.9. mg.

As described in Part I of this report, tongue signs and distension often appeared in patients who were otherwise improving, and these two signs were not considered to be unfavourable. Complete remission was indicated by

(1) Weight within 10 lbs. of normal.
(2) Stools normal in number, colour, and fat content.
(3) Absence of distension and tongue signs.
(4) No relapse on ordinary diet.

DIET.

The composition of the diets used is shown in Table I. Diets 3, 4, and 5 are based on those designed by Napier. Investigation diets 1 and 2 were similar to the Napier 4 and 5 diets respectively, but as yeast extract and liver were excluded, the vitamin content was lower. Except in patients who were the subjects of balance experiments (as described in Part II of this report) the diets were only adhered to approximately.

Of the 62 cases, 10 were severe enough to require immediate liver therapy ; 15 made slow progress and were later given liver therapy ; 14 were improving, but still had symptoms when evacuated to U. K. It is likely that in many patients of this last group complete remission would have occurred during a longer period of observation. The remaining 23 cases were discharged in complete remission and apparently cured, so that at least a third of our cases showed complete remission in the course of two to three months on dietary therapy alone. It is not possible to decide whether rest, regular meals, or the actual diet used was responsible for the improvement ; since however in order to obtain the most rapid and consistent results the therapy of sprue will generally include parenteral liver or some analogous drug, it is more important to decide the relative importance of dietary control than to determine whether the improvement noted in the 23 cases quoted above was "spontaneous" or the result of dietary control. In the controlled diets used the following factors may be discussed.

(1) Calorie value.
(2) Fat, carbohydrate and protein content.
(3) Vitamin content.

Calorie Value. The calorie value of the diets ranged from 1500 to 2600 calories. Patients with complete anorexia and copious watery diarrhoea were were not even able to take the full 1500 calorie diet, but after beginning liver therapy all patients were able to take either the 2,000 or the 2600 calorie diet, and most of them gained weight on the higher diet at a rate of up to 4 lb. a week. The calorie value of the diet which such patients can take is to some extent limited by their tolerance for fat and carbohydrate, even when their appetite is good, so that it is often usafe to allow a patient to eat as much as he wants, since a return of intestinal symptoms may be precipitated.

Fat content. For any given patient the fat content of the diet determines the degree of steatorrhoea, as has been shown in Part II of this report ; with a minimal fat intake the steatorrhoea disappears, and within the limits of a a moderate fat intake of 65 to 96 g. per day the proportion of fat absorbed is fairly constant, varying from 50 to 90% in different cases, so that, other things being equal, more fat is absorbed when more is given. From the therapeutic point of view this is important, since apart from its high calorie value dietary fat contains the fat soluble vitamins. On the other hand it is also true that the more fat there is in the diet, the more there is in the faeces, and while theoretically a high intake may be desirable in a patient who only absorbs a proportion of his intake, the amount that can be given is limited by the degree of steatorrhoea that can be tolerated. Steatorrhoea produces symptoms in two ways. Firstly, the amount of soaps in the bowel depends directly on the amount of fat, and, unless calcium is added to the diet, these soaps consist partly of sodium and potassium soaps which are soluble and irritant and produce diarrhoea.

The diarrhoea may be quite severe and lead to a rapid deterioration in the patient's general condition. Secondly the presence of much fat in the bowel by reason of its Dietary Supplements used. (Patients not on parenteral therapy.)

TABLE II

Dietary Supplements used. (Patients not on parenteral therapy.)

	Complete Remission.	Incomplete Remission.
Diet : Napier, without supplement, ..	0	0
with cooked liver, 4 oz. daily. ..	12	5
with yeast & liver. ..	10	8
Diet : "Investigation." Without supplement	1	0
With yeast extract. ..	0	1
Total : ..	23	14

The 37 cases shown in this table represent the number of patients out of a total of 62, who did not require parenteral liver therapy.

Bulk exacerbates the symptom of distension. In practice we found that our patients did not tolerate a faecal excretion of fat greater than 25-30 g. per day. We did not try giving calcium to improve the fat tolerance. *Carbohydrate Content.* It is well known that the absorption of carbohydrate is defective in sprue though this defect can be demonstrated only by blood curves and not by balance studies, since unabsorbed glucose derived from the digestion of dietary carbohydrate is to a great extent fermented by the bacteria in the colon ; thus it is not known whether fat and glucose absorption defects parallel one another in a given case. Unabosrbed glucose, like unabsorbed fat which has been changed into soluble soaps, is not inert and may cause flatulence and distension as the result of fermentation ; it is not known whether the breakdown products of carbohydrate fermentation may cause diarrhoea, but this is a possibility. Thus, the amount of carbohydrate as well as the amount of fat which may be given to sprue patients is limited by the possible appearance of symptoms of relapse.

It has been suggested (Stannus, 1942, Maegraith et al, 1945) that fructose be well absorbed in sprue, but we have obtained evidence to the contrary (to be published). The virtues claimed for strawberries and bananas in the treatment of sprue would have to be explained in some other way than by their high fructose content.

PROTEIN CONTENT

Protein is the only class of food which is well absorbed in sprue ; even in case with diarrhoea the increased loss of nitrogen in the faeces is no more than can be accounted for by the increase in intestinal secretions. Hence the amount of protein which can be given to patients with sprue is limited only by their appetite. As far as possible in our cases the protein intake was maintained at 140-150 G. per diem. The possible virtues of the high protein diet are threefold. Firstly protein supplies a source of energy in an absorbable form. Second-

TABLE III

EFFECT OF 12 DAYS PARENTERAL LIVER THERAPY IN SPRUE

Case No.	Liver Preparation Used.	Maintenance doses	Av. Cal. intake during 12 days before beginning liver.	Av. Cal. intake dursing 12 days on liver.	Normal Weight.	Weight before beginning liver.	Weight after 12 days liver	Appetite		Tongue		Diarrhoea	
								Before	After.	Before	After	Before	After
2	T.C.F.	2 c.c.	2,080	2,040	164	134	136	Poor	Good	Sore	N	—Absent—	
4	,,	,,	2,080	2,060	150	130	130	Good	Excessive	—N—		Present	Present
5	,,	,,	2,050	2,360	123	115	112	—Good—		—N—		Present	Present
6	,,	,,	2,670	2,620	140	136	136	—Good—		—N—		—Absent—	
8	,,	,,	2,260	2,675	139	122	126	—Good—		Sore	N	—Absent—	
10	,,	,,	2,460	2,280	152	126	130	—Good—		—N—		—Absent—	
11	,,	4 c.c.	1,380	1,600	155	88	97	Poor	Good	—N—		Present	Absent
12	,,	,,	2,220	2,220	148	129	132	—Good—		—N—		—Absent—	
14	,,	,,	1,780	2,000	134	112	114	—Good—		—N—		—Absent—	
15	,,	,,	2,320	2,410	144	126	131	—Good—		—N—		—Absent—	
17	,,	,,	2,380	2,373	94	110	109	—Good—		—N—		—Absent—	
18	,,	,,	2,170	2,420	158	114	120	Poor	Good	Sore	N	Present	Absent
19	,,	,,	..	1,585	140	84	85	Poor	Good	Sore	N	—Absent—	
20	,,	,,	2,360	2,550	146	130	136	—Good—		—N—		—Absent—	
23	Hepastab	,,	2,370	2,480	130	114	116	Poor	Good	—N—		—Absent—	
24	,,	,,	2,490	2,510	144	136	140	—Good—		—N—		—Absent—	
25	,,	,,	1,970	1,600	142	105	106	Poor	Good	—N—		Present	Absent
												(Sulphaguanadine Given.	

Note : 1 All patients received 10 c.c. of liver daily for 4 days at the beginning of treatment, followed by the daily maintenance dose shown.
2. N=normal.

ly protein is required for the replenishment of the body stores of protein which are depleted in many patients with sprue, as evidenced by the generalized muscular wasting and the low plasma protein levels. Thirdly, the high protein diet may be a source of a food factor deficient in sprue and shown below to be present in liver and yeast extracts. That protein is well absorbed and utilized in sprue patients in remission is shown by the positive nitrogen balances found in such patients (as shown in Part I of this Report).

VITAMIN CONTENT

The vitamin content of the diets other than the two "Investigation" diets was greatly modified by the inclusion of cooked liver (4 oz. daily), yeast extract in the form of 'Vegemite' (2 teaspoonsfull daily), or yeast food (1 oz. daily). In 36 out of the 37 patients who improved without parenteral liver therapy, these supplements were included in the diet, as shown in Table II. We obtained no adequately controlled data on the clinical effect of yeast extract (Vegemite) by mouth. This substance was given either to the mildest cases who did not require parenteral liver or to severe cases after usually prolonged therapy with parenteral liver. It is shown in the second part of this section that the yeast extract when given by mouth in large doses (20 g. daily) rapidly improves fat absorption in some patients and for this reason alone it may be considered a useful adjunct to therapy. On the other hand it is unpleasant to take in such large quantities and in some patients produces flatulence and heartburn.

RESULTS OF PARENTERAL THERAPY

Controlled observations on the effect of different forms of parenteral therapy in sprue were made on those patients who were also the subjects of balance experiments. In these patients the prescribed diets ("Investigation" 1 and 2) were either rigidly adhered to or else any deviation from the set diet were and recorded from day to day. The diets contained no liver or yeast.

EFFECT OF NICOTINIC ACID AND RIBOFLAVINE

Perhaps because the tongue lesions in sprue sometimes resemble those of pellagra or sometimes those reported in riboflavine deficiency, nicotinic acid and riboflavine have been used and recommended (Manson-Bahr 1944) in the treatment of sprue, though there appear to be no controlled observations on the effects if these substances in sprue. In the course if experiments on the effects of these substances on fat absorption, reported later, we were able to make obsertions, reported later, we were able to make observations on their clinical effect. Very few if our cases had wellmarked tongue lesions, and the only common lesion was a slight reddening at the tip and sides accompanied by soreness. Six patients received nicotinic acid (50 mg. t.d.s.) and riboflavine (5 mg. daily) parenterally. All but one were more than 20 lb. under weight. In three the appetite was poor and two complained of sore tongue at the time of begining the treatment. All had steatorrhoea but none had water diarrhoea. At the end of a twelve day trial of this combination of drugs there was no significant change in any of the patients as regards weight, appetite, and tongue symptoms ; the steatorrhoea was not improved and possibly made worse. Two more patients who were given nicotinic acid similarly failed to respond.

EFFECT OF PARENTERAL LIVER

Parenteral liver therapy was ultimately given to all those patients who did not respond satisfactorily to diet and rest alone. The results of such treatment, using "T.C.F." (an Indian preparation) or "Hepastab" (Boots) are summarized in Table III. These preparations are not crude but they were for a long time the only ones available to us. The 17 cases represented in Table II were all on a known diet, and received four daily doses of 10 c.c. of liver extract followed by either 2 or 4 c.c. daily. In some this treatment was preceded

TABLE IV

Weight changes (in lb) during 12 days on parenteral liver therapy, grouped according to the Calorie intake and according to the presence or absence of diarrhoea at the beginning of treatment.

	Calorie intake : 1650-	1650-2100	2100
Cases without diarrhoea.	(19) : +1	(2) : +2	(8) : +4
		(14) : +2	(10) : +4
			(12) : +3
			(15) : +5
			(20) : +6
			(23) : +2
			(24) : +4
Cases with diarrhoea	(11) : +9	(4) : 0	(5) : 3
	(25) : +1		(18) : 6

Note :—The numbers in parentheses denote individual patients in the series.

by treatment with nicotinic acid and riboflavine, shown above to be ineffective ; in such cases the vitamin therapy was continued during the trial of liver. Other deviations from the standard treatment are shown in the table. The effect of treatment was assessed by changes in weight, appetite, tongue symptoms and diarrhoea at the end of a twelve day period. The appetite was improved in all 6 patients who had been complaining of poor appetite, and soreness of the tongue disappeared in the 4 patients who had been complaining of this symptom. Five of the patients had watery diarrhoea when on liver therapy alone. These results may be compared with the known effects of crude liver extracts (Castle and Rhoads 1935 ; Rodriguez-Molina 1943) which in sprue cases improve the appetite regress the tongue lesions and frequently arrest the diarrhoea. These effects have been attributed to the replacement of an unknown factor deficient in sprue patients. It is interesting to note that these effects were to some extent reproduced in our patients with relatively purified liver extracts. The weight changes are analysed separately in Table IV, in which patients 6 and 17 are not included since their weight was normal at the beginning of the trial. The remaining fifteen patients are grouped according to their dietary intake and according to whether or not they had diarrhoea at the beginning of the trial. The patients without diarrhoea responded roughly according to their calorie intake, in that there was no significant again in weight in the four patients whose calorie intake was less than 2,100 Cals, per day, while the seven patients whose intake was over 2,100 Cals. showed an average weight gain of 4 lbs. during the first 12 days of liver treatment. In the patients with diarrhoea the weight response was variable. There was no response in those patients in whom the diarrhoea was not arrested (cases 4 and 5) ; with arrest of diarrhoea case 18, on a 2,400 Cal. intake, gained 6 lb. in weight, case 25 gained only 1 lb. but was on a 1,600 Cal. diet, case 11 gained 9 lbs. on a similar intake, but a lot of this gain was due to water retention, subsequent to the arrest of the diarrhoea.

In spite of the weight gain shown by these patients when on an adequate diet, liver therapy (using the semipurified extracts) could not be shown to improve fat absorption in a twelve day period, though it did so over longer periods of treatment.

Details of the clinical changes with parenteral liver therapy are given in summary form :

(1) Mental.—Subjective improvement (1-2 days).

(2) Skin—Change from pallor to pink (2-3 days) ; later scaling may be be marked (6-12 days).
(3) Alimentary Tract—
  (a) Appetite improves ; vomiting stops ; (4-6 days).
  (b) Tongue : slight if any glossitis etc. (4-6 days).
  (c) Diarrhoea stops (6 days) ; stools formed, bulky, yellow.
  (d) Abdominal distension increases (1 week onwards), with cessation of diarrhoea.
  (e) Gastric juice ; restoration of HCI in two histamine-fast achlorhyrics (1-2 months).
  (f) Barium meal : in one instance change from gross bolus formation to normal appearance of mucosal pattern occurred in 4 weeks.
(4) Weight gain-begins during tue first week ; persists.
(5) Weakness diminishes (1-2 weeks)
(6) Blood pressure increases from hypotension (1-5 weeks).
(7) Blood : macrocytic anaemia respinded slowly using T.C.F.

TREATMENT OF SPECIAL SYMPTOMS

DIARRHŒA

The commonest sympton requiring special treatment in sprue is diarrhoea, when it does not respond to parenteral liver therapy. Diarrhoea is often simply due to dietary excess and is relieved when the carbohydrate and fat content of the diet is reduced, but the very severe cases often have a copious water diarrhoea

TABLE V.

RECOMMENDATIONS FOR THE TREATMENT OF THE VARIOUS TYPES OF ACUTE SPRUE

Type of case	High protein diet, Napier 1—5 + oral liver (cooked).	Parenteral liver 10 c.c. daily for 4 days ; then 4 c.c. daily.	Sulphaguanadine 7 g. stat, then 3, 5 g. 4 hourly total=70 g.	Sodium chloride 10 g. daily.	Blood transfusion
Acute Sprue mild					
(a) In remission	+	−	−	−	−
(b) Static or in relapse.	+	+	±	+	+
Acute Sprue severe	+	+	+	+	±
Acute Sprue with Severe anaemia	+	+	+	−	+

+ Indicated
± Indicated in certain cases
− Not indicated.

though taking miniamal amounts of food. These cases may become severely dehydrated owing to salt deficiency. We have found that in these cases the diarrhoea may be arrested by combining a course of sulphaguanidine with parenteral liver therapy. Sulphaguanidine also frequently controls diarrhoea in sprue without added liver therapy, but the effect is transient and the diarrhoea often returns when the drug is discontinued. The beneficial effect of sulphaguanidine in spure is surprising since no pathogenic microorganisms can as a rule be isolated in these cases, and it must be assumed that the drug acts by inhibiting the growth of bacteria which are normally not pathogenic but which assume a pathogenic role in the sprue patient. It is reasonable to suppose that the atrophic intestine of the sprue patient might show a diminihed risistance to bacterial irritants. This would explain why the diarrhoea may be controlled by sulphaguanidine but relapses unless parenteral liver therapy is given at the same time, since sulphaguanidine would not effect the mucosal atrophy.

SALT DEFICIENCY

As shown in Part II of this report, a deficiency of salt is the cause of the dehydration with hypotension which may be found in the worst cases of sprue. This is partly due to the exessive loss of electrolytes in the copious water stools and partly to the diminished intake of salt associated with a small for intake. In these cases efforts to control the diarrhoea must be combined with treatment of the water and salt deficiency. Patients may be made to take from 10 to 15 g. extra sodium chloride daily, and for this we have found lemon squash a good vehicle.

ANÆMIA

As shown in Part I of this report, few of our patients were seriously anæmic. In those whose response to TCF was not satisfacotry and when the red cell count was below 2 millions per c.m.m. a transfusion of whole blood was given. In three patients to whom this treatment was given there was rapid improvement in the patients' condition, but one of the patients required more than one transfusion (Case 4 in Fig. 7 of Part I of this Report). The impression was gained that some factor other than the red cells plasma co mponents exerts a "trigger" effect, whereby red cell production is markedly increased and other tissues e.g. the alimentary tract are beneficially affected.

GENERAL MANAGEMENT OF THE SPURE PATIENT

From the observations and conclusions outlined above certain principles in the treatment of sprue may be given. The indicators for the various forms of treatment are shown in tabular form in table V.

Except in the very mildest cases, and certainly in any patient with loss of weight, hospital treatment is indicated, because rest is important in this disease and, inspite of the benefits if parenteral liver therapy, dietary control is essential of efficient treatment. The diets should have a low residue and the food be given regularly. For the patient with a capricious appetite it is important that the food should be well prepared. The diets designed by Napier have proved very useful. In the severe cases in relapse Diet 3, and in the milder cases Diets 4 and 5 have been used. The patient should take the highest diet possible without producing symptoms of relapse, of which the most important is diarrhoea. Weight gain is not assured until he is able to take diet. 5

Parenteraly liver therapy is in many cases essential to the success of dietary therapy and hastens recovery in all cases. In many patients an increase in dietary intake would be impossible without parenteral liver. Large daily dosses must be used, and the extract should be crude, though good results are obtained with semipurified extracts. Occasionally parenteral liver and dietary control fail to arrest the watery diarrhoea and in these cases sulphaguanidine has proved invaluable. These cases may be complicated by dehydration due to

salt deficiency, and this condition calls for urgent treatment. In cases with severe anaemia a transfusion may be required to initiate recovery.

Fat absorption improves slowly on this regime, using semi-purified liver extracts and as in many cases yeast extract by mouth accelerates the improvement in absorption it is a useful adjunct to therapy. It has to be given in rather large dosse which some patients find unpleasant to take.

After 8 to 12 weeks on this regime most patients are apparently in complete remission but we have no data on the relapse rate.

SECTION II

EFFECT OF THERAPY ON FAT ABSORPTION

Using the fat balance technique described in Part II of this Report, a study was made of the effect of various substances on fat absorption in sprue. The 23 patients selected for this investigation had all failed to improve on dietary therapy alone. Because of the variability of fat output over short periods, conclusions are based on results grouped into 12 day periods, except in a few cases specified in the tables, where treatment had to be begun early or the patient left hospital. Interpretation of the results must take into account the possibility of spontaneous improvement. This consideration does not affect the interpretation of negative results of treatment. In the case of yeast extract, in which early results suggested a positive action on fat absorption, we used in the later cases a double pre-period, so that any spontaneous improvement which was going to occur might become apparent. Minor difficulties in interpretation arise from the occasional incidence of water diarrhoea, from the change in some patients from a 65 g. fat diet to a 96 g. fat diet, and from the possibility that part of the faecal fat is a true excretion and not unabsorbed food fat. Patients with watery diarrhoea were excluded from the series until the diarrhoea had been controlled by liver treatment or sulphaguanidine ; watery stools with solid particles cannot be fairly sampled, and diarrhoea itself affects fat absorption. With regard to dietary variation, it was found that change of diet from 69 g. to 96 g. of fat per day did not affect the percentage fat absorption enough to interfere with interpretation of fat balance results (Part II of this Report). It was also found that on a fat free diet sprue patients excreted no more fat than normal subjects, so excreted as opposed to unabsorbed fat represents only a small systematic error which does not affect significantly the comparison of successive periods.

Effect of Nicotinic acid and Riboflavine. Table VI gives the fat absorption figures in two patients treated with nicotinic acid 50 mg. t.d.s., and in four patients treated with nicotinic acid 50 mg. t.d.s., and riboflavine 5 mg. daily ; these drugs were given intramuscularly. In none of the six patients was there any significant change in fat absorption ; taking the series as a whole, there was a small drop in fat absorption in five of the six patients. The figures for the four patients who had both nicotinic acid and riboflavine were analysed together, and the probability of the fall being due to chance is 0.1. There was therefore no evidence that nicotinic acid and riboflavine improved fat absorption, and a strong suggestion that fat absorption actually deteriorated to some extent. Since the two cases treated with nicotinic acid alone also showed a deterioration of the same order, it seems likely that in the combination of the two drugs it was the nicotinic acid which was responsible. As shown earlier in this section there was no clinical improvement with nicotinic acid or riboflavine. These results conflict with the claims of Manson-Bahr (1941). As stannus (1942) points out, most of Manson-Bahr's cases were having liver treatment at the same time as nicotinic acid, and this could account for the improvement which he observed. While it is possible that nicotinic acid or riboflavine may have a favourable effect on the tongue lesions in cases with well established

secondary deficiencies of these vitamins our own results suggest that the fundamental anomaly in sprue, the failure of fat absorption, is not influenced by such therapy. Intensive therapy with single vitamins may even be harmful, by accentuating a multiple vitamin deficiency-'vitamin inbalance' (Morgan, 1941).

Effect of liver Extract. The value of liver extract in the treatment of sprue is well established and as far as clinical improvement is concerned this was confirmed in our cases. Barker and Rhoads (1937) found that large doses of crude liver extract given by injection improved the absorption of fat in sprue as judged by the serum lipid curve after a fatty meal. S rum lipid curves are open to some criticism, in that the normal range is wide, and also they can measure only the rate of fat absorption, and not the total amount absorbed (Part II of this Report). We have observed the effect of liver extracts on fat absorption by the balance technique in eight patients, four of whom were used for more than one trial, so that Table VI gives the results oft welve such experiments, each based on 2 successive 12-day periods. Three liver extracts were used

(1) 'T.C.F.' An Indian preparation, the only one available to us for some months, described as containing 'most of the B complex substances present in the original liver.' It was semipurified and though certainly not so crude as the preparation used by Rodriguez-Molina, each c.c. of which was derived from only 5 grams of fresh liver, it was found to be effective in the clinical treatment of sprue.

(2) 'Hepastab' (Boots). A moderately refined extract.

(3) 'Hepatex-T' (Evans). An extract containing the whole of the vitamin B complex naturally contained in liver, and also added thiamine and nicotinic acid. This preparation is designed for the treatment of tropical macrocytic anaemia.

The standard dosage used was 4 c.c. daily for all preparations, and in all cases a loading dose of 40 c.c. spread over 4 days was given at the beginning of liver treatment ; all doses were given intramuscularly. When Hepastab and Hepatex-T became available, they were used in order to see whether they would produce an improvement in fat absorption which we had failed to find with the less well defined Indian preparation. With the exception of one trial of Hepatex-T (Patient 20), there was no significant improvement in fat absorption, and the improvement of 12.2% in one case out of eight, though statistically signi-

TABLE VI

Effect of nicotinic acid and riboflavine on fat absorption.

Patient No.	Period 1.		Period 2.		Difference % F.A. between the periods.
	Duration (Days)	% fat absorption	Duration Days()	% fat absorption in	
6	12	79.9	9	74.8	−4.7
9	12	79.8	8	70.4	−9.4
12	12	89.4	12	79.8	−9.6
14	12	77.2	12	75.2	−2.2
15	12	80.0	12	73.6	−6.4
17	12	79.2	12	82.3	+3.1

Note :—Period 1 in all cases was without treatment. In period 2, all patients were given 50 mg. nicotinic acid t.d.s. . in addition, patients 12, 14, 15 and 17 were given 5 mg. riboflavine daily.

TABLE VII

Effect of liver extract on fat absorption in successive 12 days periods.

Patient No.	Treatment.	% fat absorpt	Treatment	% fat absorptn.	Difference in % fat abs. between the periods.
2	None	50.7	TCF	47.0	−3.7
24	None	79.6	TCF	81.0	+1.5
23	None	88.5	H'stab.	82.0	−6.2
12	Nic, Rib.	79.8	Nic, Rib. TCF	83.0	+3.9
15	Nic, Rib.	73.6	Nic, Rib. TCF	78.0	+4.4
17	Nic, Rib.	82.8	Nic, Rib. TCF	83.4	+0.6
14	TCF	57.2	H'tex-T TCF	60.4	+3.2
15	TCF	78.0	H'tex-T TCF	79.6	+1.6
17	TCF	83.4	H'tex-T TCF	82.9	
20	TCF	69.9	H'tex-T TCF	82.1	+12.2
12	TCF	82.8	H'stab TCF	87.5	+4.7
24	TCF	81.0	H'stab TCF	81.8	+0.8

Note :—Nic. is an abbreviation fir nicotinic acid, Rib. for riboflavine, H'stab for Hepastab, and H'tex-T for Hepatex T. The dosage of liver is given in the text ; patient 2 had ml. of TCF daily instead of the standard 4 ml.

ficant, could easily have been spontaneous. (cp. Part II of this Report.). Bassett et. al. (1939) also failed to demonstrate any improvement in fat absorption with liver treatment of idiopathic steatorrhoea.

These negative results stand in very marked contrast to the striking clinical improvement shown by our patients on liver treatment. They gained weight rapidly, their appetite improved, tongue signs disappeared, and they felt much better. Liver extract also improved diarrhoea in many of those patients who had it ; for reasons already given, such patieuts have not been included in the fat absorption series. Moreover, we found that patients who were kept on liver treatment for a month or more showed gradual improvement in their fat absorption (Table VIII). The striking thing however is that with doses of liver extract sufficient to produce a rapid clinical improvement there is so small and gradual effect on the fat absorption defect. This finding will be discussed later in relation to our results with yeast extract.

Yeast Extract. The preparation used was 'Vegemite', which resembles Martime and is manufactured in Australia. It was given in a dose of 5 grams four times a day. The effect of treatment with yeast extract on fat absorption is shown in Table IX. In all cases, the patients who were given the yeast extract

were also on either 4 c.c. or 2 c.c. of liver extract daily ; the reasons for this procedure as as follows :—

1. It h as already been shown that liver extract in the dosage used given over a period of less than a month does not improve fat absorption demonstrably, so that any observed improvement within this period can be ascribed to the added yeast extract.

2. As far as possible, severely ill patients were chosen for this study, to lessen the chances of spontaneous improvement. Such patients are liable to diarrhoea, with rapid deterioration in their general condition, and such relapses can be controlled or prevented by liver treatment.

TABLE VIII

Effect of continued liver treatment (5-7 weeks) of fat absorption.

Patient No.	Period 1. (Pre-treatment) % fat absorption.	Period 2. (after 5-7 wks. liver) % fat absorption.
4	75	79
11	61	77
14	75	81
15	80	79
17	79	83
19	77	84
20	70	82
24	80	87
Means	74.6	81.5
S.D.	6.44	±3.21
Difference between means		609
Standard error of difference		±2.44

The difference between the means is statistically significant.

3. Since no yeast extract suitable for parenteral injection was available to us, liver extract was given to insure that any favourable action of yeast extract should not be prevented by a secondary absorption defect, such as may occur in sprue and be amenable to liver therapy.

Of the 12 patients represented in Table IX, the first six were put on yeast extract after 32 days or less on liver treatment, and their fat absorption in the first preliminary observation period ranged from 62% to 80%%. All the other six patients had liver for a longer period before yeast extract was started, and their initial level of fat absorption also tended to be higher, and in two cases was over 80%. The patients were studied over 3 consecutive periods, each of 12 days where possible. They received yeast during the third period, but were otherwise on the same regime as in the two preceding control periods (except in respect of nicotinic acid in patients 3 and 6). From the first period to the second period there was often a slight but not significant improvement. From the second to the third period there was a marked improvement in fat absorption in the first six patients as shown in Table IX, which was significant for the six patients taken together. In the second group of six patients, who had been receiving liver therapy for a longer period, and whose fat absorption defect was in general less severe, yeast extract did not produce any detectable improvement except in one (patient 27) whose fat absorption had remained at a low level inspite of fairly prolonged liver treatment.

TABLE IX

EFFECT OF YEAST EXTRACT ON FAT ABSORPTION

Patient No.	Duration of liver treatment before giving Years. (Days].	First preliminary period.			Second preliminary period.			Yeast extract period		Difference in % fat absorption between periods.	
		Duration (days)	Treatment	% fat absorption	Duration (days)	Treatment	% fat absorption	Treatment	% fat absorption	(2—1)	(3—2)
3	0	6	None	73.0	12	Nic.	68.8	Nic, Rib. Liver, Y.	83.1	−4.2	+14.3
6	0	12	None	79.5	12	Nic	83.5	Nic, Rib. Liver, Y.	90.5	+4.9	+17.0
8	0	9	None	80.2	11	None	80.8	Nic, Rib. Liver, Y.	85.5	+0.6	+ 4.7
25	14	8	Liver	72.7	8	Liver	68.6	Liver, Y.	72.8	—4.1	+ 4.2
28	28	12	Liver	65.8	12	Liver	69.0	Liver, Y.	80.4	+3.2	+11.4
2	32	12	Liver	62.2	12	Liver	64.6	Liver, Y.	71.6	+2.6	+ 7.0
4	37	12	Liver	73.8	12	Liver	79.4	Liver, Y.	82.3	+5.6	+ 2.9
24	43	12	Liver	83.5	12	Liver	86.6	Liver, Y.	87.2	+3.1	+ 0.6
27	45	12	Liver	64.8	12	Liver	63.2	Liver, Y.	68.7	−1.6	+ 5.5
17	47	8	Liver	89.4	8	Liver	87.2	Liver, Y.	86.1	−2.2	− 1.1
15	49	8	Liver	76.4	8	Liver	80.7	Liver, Y.	81.1	+4.3	+ 0.4
14	63	8	Liver	74.7	8	Liver	83.6	Liver, Y.	84.1	+8.9	+ 0.5

Notes : Abbreviations as in Table VII Y.=Teast extract. All the yeast extract periods were of 12 days.

The results suggest that the yeast extract contains a factor which, in the doses used, improves fat absorption in many sprue patients. The results on the second group of six patients suggest that long-continued liver treatment may, even with semi-purified extracts supply an adequate dose of factors similar to those in the yeast extract. While the yeast extract improved the fat absorption in most patients, it did not always bring it back to normal in these patients, suggesting that its action is a form of replacement therapy rather than curative. Bigger doses could not be tried as the extract is unpleasant to take in large quantities. No adequate observations were made to determine whether the yeast extract has the same beneficial effect on the tongue lesions and weight loss of sprue as parenteral liver extract.

Finally, it has to be noted that, as shown earlier in this section, a large proportion of the patients in our series returned to normal without any form of parenteral therapy, on a diet of high protein content which usually included cooked liver or yeast extract. In these patients the steatorrhoea disappeared gradually or suddenly after a variable period in hospital and it was not possible to attribute this change to any known factor in the treatment.

SECTION III

DISCUSSION

The results of various forms of therapy in sprue may be interpreted in the light of recent observations (Spies et al. 1946 Darby et al., 1946) on the effect of folic acid in sprue. This substance, present in liver extracts, has a dramatic effect on some of the symptoms of sprue. In particular it is said to relieve diarrhoea and tongue lesions and to produce a rapid gain in weight, and it cures the macrocytic anaemia of sprue. This suggests that it has an effect comparable to that of parenteral liver extract in this disease. The beneficial effect of liver extract may be due to its folic acid content and this is consistent with the statement (Lancet 1946) that folic acid is not 'Haemopoietin', since highly purified extracts with maximal haemopoietic activity are recognised to be relatively ineffective in sprue. Like parenteral liver extract, folic acid apparently does not improve the steatorrhoea of sprue. Whether all the effects of liver are reproducible with folic acid is not certain ; in particular, the weight gain reported to occur with folic acid therapy may be a result simply of the arrest of diarrhoea. Our patients gained weight rapidly with liver extract, while remaining on the same dietary intake, and whether they had diarrhoea or not, so that the effect could not be attributed to the correction of dehydration.

As shown in Part II of this Report, patients in remission were in marked positive nitrogen balance, suggesting that they had at one time been in negative nitrogen balance, though absorption of nitrogen is generally not impaired in in sprue. It would seem that patients with sprue are unable, in the "relapse" phase, to utilize properly absorbed nitrogen, and the weight gains recorded with liver therapy may be due to the correction of this metabolic abnormality by the provision of a deficient vitamin-like factor. There is experimental evidence that such a factor is necessary for normal plasma protein production (Madden et all 1945) Before it can be stated that folic acid duplicates the effects of liver in sprue it has to be shown that this vitamin produces weight gain on a controlled diet in patients without diarrhoea. The beneficial effect of oral yeast extract on fat absorption is not likely to be due to folic acid, since parenteral liver extract, which contains folic acid, does not improve fat absorption. Moreover the few observations there are on the subject do not suggest that folic acid itself improves fat absorption. No balance studies to determine the effect of folic acid on fat absorption have so far been reported.

The known facts suggest that there are several distinct deficiencies in the genesis of the sprue syndrome. They are not all of the same relative importance in the study of the aetiology of the disease. In its simp.est form sprue appears

as steatorrhoea, usually with loss of weight. Tongue changes, anaemia, diarrhoea appear later. The fat abosrption defect responds in some measure to yeast extract and to large doses of crude liver extract. Weight gain in the uncomplicated case may be produced by parenteral liver extract and possibly by folic acid. Folic acid relieves the tongue symptoms, anaemia and diarrhoea. As a provisional hypotehsis it is suggested that folic acid deficiency is a common secondary deficiency in sprue, comparable to other secondary deficiencies seen in this disease, and that the basis of the primary absorption defect has not been discovered. The absorption defect may be related to an unknown substance present in crude liver and yeast extracts. Known secondary deficiencies have been uncommon in our series, but it is well recognized, that deficiencies of nicotinic acid, riboflavine, vitamin K, and probably vitamin A, as well as of minerals such as cal cium and iron may occur. These deficiencies may be due to both diminished intake and deficient absorption or even to a change in the synthesis of vitamins in the bowel (Leishman 1945). They respond well to appropriate therapy. Manson-Bahr has even claimed that nicotinic acid alone may cure sprue. In cases uncomplicated by secondary deficiencies, however, our resu.ts appear to demonstrate that neither nicotinic acid nor riboflavine has any curative value, and that the beneficial effect of nicotinic acid is probably important only in so far as it relieves or prevents symptoms of pellagra, such as the more severe types of glossitis seen in classical sprue. Glossitis is common in deficiency states, and of manifold causation so that in a disease like sprue which may be compli cated by a variety of deficiency states different forms of glossitis may be seen including those attributed to nicotinic acid and to riboflavine deficiency.

An alternative view of the genesis of the sprue syndrome, while still attributing some of the classical symptoms to secondary deficiencies, would assume that folic acid deficiency is of primary importance in the production of the syndrome. Though early cases do not show all the abnormalities which are corrected by folic acid in humans, a constant feature of the clinical history of these patients is the presence at some time of recurrent mild diarrhoea, usually not of dysenteric aetiology It is conceivable that this diarrhoea is itself a sign of folic acid deficiency, since Carruthers (1946) has shown that a variety of types of chronic diarrhoea in the tropics can be relieved by folic acid therapy. This view would imply that folic acid deficiency leads in some way to a fat absorption defect which is not remedied when the folic acid deficiency is corrected. There is in fact not yet sufficient evidence to define the role of folic acid in the absorption defect which appears to be the fundamental abnormality in tropical sprue.

The results presented in this Report show that sprue, as manifested by steatorrhoea and loss of weight, may exist in the absence of other signs of disease. Many of these signs probably result from secondary deficiencies, yet it is often only in the presence of these other signs, such as anaemia, diarrhoea and severe glossitis, that tropical sprue is in fact diagnosed, while the current methods used for demonstrating steatorrhoea, on the basis of the percentage composition of the faeces, are inaccurate and inadequate. Since treatment is in general likely to be more successful when given early in the disease, the diagonisis should be made at an early stage. All cases of persistent diarrhoea and loss of weight, especially if arising during the hot season, should be investigated for steatorrhoea. Cases of proved bacillary and amoeaic dysentery may develop sprue and so fail to respond to antidysenteric treatment and they represent the commonest missed diagnosis of sprue. While with a low-residue diet containing 60-90 grams of fat per day a faecal fat content exceeding 30% of the dry weight may be taken to indicate steatorrhoea, a lower fat content does not exclude steatorrhoea. In doubtful cases a limited fat balance study over a three or four day period is essential to establish the presence or absence of steatorrhoea. Facilities for this type of investigation were not in general available, but the importance of the proper investigation of steatorrhoea must be stressed, because treatment

in the early stages if this disease, in the absence of complicating secondary deficiencies, is relatively simple and effective.

SECTION IV

SUMMARY

The results of treatment in tropical sprue were assessed clinically in 62 patients. They were young soldiers with short tropical service and where mostly suffering from a mild type of the disease. Treatment was based on a series of diets of high protein, low fat content, with in addition cooked liver or yeast extract. On this regime 23 of the patients showed complete remission and 14 were improved. The remaining 25 patients required parenteral liver therapy.

The results of parenteral therapy with nicotinic acid, riboflavine and liver extract respectively were assessed on patients who were not improving on diet alone. These patients were put on to a carefully controlled "investigation" diet which did not include oral liver or yeast extract, and fat balance studies were made in parallel with clinical observations. Parenteral nicotinic acid and riboflavine were of no benefit in our cases, in whom specific secondary vitamin deficiencies were rarely seen. Semi-purified liver extracts were effective in controlling the symptoms of the disease and produced a rapid gain in weight in patients whose colorie intake exceeded 2,100 Cals. daily. Diarrhoea, when present, often stopped with this therapy, but occasionally sulphaguanidine had to be given in addition to parenteral liver and was found to be effective in controlling this symptoms.

Clinical improvement was not related to improvement in fat absorption. With the parenteral liver therapy used fat absorption improved only slowly. Nicotinic acid and riboflavine did not improve absorption. A separate study was made of the effect of a yeast extract ("Vegemite") of fat absorption when given orally (5 grams q.d.s.) in conjunction with parenteral liver extract With this substance an improvement in fat absorption could be demonstrated in those patients who had not had prolonged preliminary parenteral liver therapy. These results are discussed in relation to recent work on folic acid therapy in sprue.

Early diagnosis, by the investigation of fat aasorption, is thought to be important in the success of treatment.

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